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Integrating the Prevention and Control of Rheumatic Heart Disease into Country Health Systems: A Systematic Review

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In loving memory of my grandfather who passed away suddenly this year.

DECLARATION

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ABSTRACT

Part A is a research protocol which describes the background and proposed methodology of this systematic review. This section contains the details of quantitative and qualitative methods to be used when analysing rheumatic heart disease (RHD) prevention and care programmes.

Part B is a literature review which expands on the protocol. An in-depth explanation of the disease process is presented in order to understand the multiple opportunities for preventing RHD and its precursors. The importance of this research then is highlighted by contextualising RHD programmes within the health system and integrated care.

Part C presents the research as a journal manuscript according the BMJ's instructions for authors. The manuscript includes a brief introduction to the research followed by a summary of the methods and presentation of the results which are then discussed.

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PART A: PROTOCOL

ABBREVIATIONS AND DEFINITIONS

Abbreviations

ARF	Acute Rheumatic Fever
BPG	Benzathine Penicillin G
GAS	Group A Streptococcus
HICs	High-income countries
INR	International Normalised Ratio
LMICs	Low and Middle Income Countries
RADT	Rapid Antigen Detection Test
RHD	Rheumatic Heart Disease
WHO	World Health Organization

Definitions

Aetiology	The cause or set of causes or manner of causation of a disease or condition.
Disability-adjusted life years	A measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death.
Endemic	Regularly found among particular people or in a certain area.
Gram-positive bacteria	Bacteria which appear violet following a gram stain as a direct result their cell wall characteristics.
Integration	The extent, pattern, and rate of adoption and eventual assimilation of health interventions into each of the critical functions of a health system.
Pathogenesis	The manner of development of a disease.
Subclinical	Relating to or denoting a disease which is not severe enough to present definite or readily observable symptoms.

1. BACKGROUND

Rheumatic heart disease (RHD) is a chronic cardiovascular condition which affects more than 30 million individuals worldwide and is responsible for about 300,000 deaths annually, therefore significantly contributing to global disability and mortality rates.[1] While the burden of RHD has mostly receded in high-income countries due to improved living conditions and advanced medical care, it remains a public health problem in under-resourced settings. Prevention and treatment of RHD has been a challenge partly due to the aetiology of this condition, which has its roots in infectious disease and an autoimmune response.

RHD is a condition which typically develops following a single severe episode or multiple episodes of acute rheumatic fever (ARF), an abnormal autoimmune response to untreated Group A streptococcus (GAS) infection.[2] Children and young adults living in poverty-stricken, overcrowded, areas are particularly susceptible to GAS infection since this type of environment facilitates the spread of the infectious agent.[3] Among those who do not seek treatment for their sore throat, 0.3-3% will develop ARF and will need to be hospitalised to treat the array of signs and symptoms.[4] Poorly managed ARF can lead to RHD and irreversible damage to the heart valves for which cardiac surgery is required.[4] Unfortunately, barriers to such surgery results in premature deaths, the majority of which, occur before the age of 25 years.[2] With an estimated 10 million disability-adjusted life years lost due to RHD globally, the economic effects are felt at both the individual and national levels.[1]

1.1 Health system considerations

Historically, disease control programmes have been delivered in a targeted, or *vertical*, manner which is currently viewed as unsustainable from a health systems perspective. However, very little evidence exists to guide the successful development of RHD programmes which are more integrated, or *horizontal*, for typically resource-constrained, endemic countries.

There are multiple opportunities to intervene along the GAS to RHD pathway which can be at the primordial, primary, secondary or tertiary level.[4] Primordial prevention includes improved living conditions and access to health care in order to limit the exposure of at-risk individuals to GAS. Reduced incidence of ARF and RHD in developed countries has been attributed to improved living conditions, with many low- and middle-income countries (LMICs) falling behind.[5,6] Primary prevention includes the treatment of GAS infection with benzathine penicillin G (BPG) to mitigate the risk of ARF.[7] Patients with ARF are prescribed a regular dose of BPG as a secondary prevention measure against recurrences and development of RHD. Registers for patients with ARF and RHD are also advantageous for this level of prevention to monitor treatment adherence and patterns of the disease.[8] At the tertiary level, once RHD becomes symptomatic, surgery to repair or replace the damaged heart valves along with long-term medical management is required for survival.

Vertical programmes are often targeted to a particular population or service which may incorporate dedicated health care professionals with specialised training at particular facilities, such as tuberculosis clinics.[8,9] These stand-alone programmes have been effective, particularly for infectious diseases, in middle-income regions such as Latin America and North Africa.[9] In contrast, a horizontal (herein referred to as *integrated*)

approach, incorporates elements of disease control into health systems and are viewed as health systems strengthening interventions.[8] Such programmes are usually linked to other services and are more widely available, providing a more holistic approach to health.[9] Funding is another distinguishing element, as vertical programmes tend to be donor funded or have dedicated, rigid, budgets while integrated programmes flow from existing health care funds.[9]

There has been a longstanding debate about which approach is superior for disease interventions, however a polarized distinction such as this is too simplistic for the reality of health care delivery. A diagonal approach incorporating elements of both vertical and integrated programmes would be well suited to tackling RHD since diagonal programmes are designed to strengthen primary health care while performing disease-specific activities.[8]

1.2 Importance of this review

Most current interventions are integrated to some degree according to health system functions; the efficacy of more- or less- integrated programmes are often comparable, despite being context dependent.[10] When thinking about the most suitable intervention for RHD care, one needs to carefully consider the characteristics of the intervention as well as the nature of the health system. Efforts to scale up RHD prevention and care has been most frequently targeted, however taking a broad view of the whole system is critical for health system planning in low-income regions with scarce resources and less robust health systems.

RHD has recently attracted global attention for being a preventable disease, to which the World Heart Federation has responded by setting a goal to achieve a 25% reduction in

premature deaths from ARF and RHD among individuals younger than 25 years of age, by the year 2025.[11] In order to achieve this, evidence-based prevention and treatment services require scaling up in the countries and regions which are still heavily burdened by RHD.

Atun and colleagues present a conceptual framework for analysing the extent and nature of programme integration.[12] Briefly, the six key functions comprise (i) stewardship and governance, (ii) financing, (iii) planning, (iv) service delivery, (v) monitoring and evaluation, and (vi) demand generation. By combining this framework with a results chain, the effectiveness of programme integration can be inferred.

This review will provide evidence on the effectiveness of integrating RHD-related services into existing health systems, with the intention of offering technical assistance to heavily burdened countries and regions.

2. OBJECTIVES

To assess integrated programmes targeting RHD prevention and control in order to evaluate the effectiveness of the extent and nature of integration within the relevant health systems.

3. REVIEW QUESTION

Are RHD prevention and control programmes more or less successful based on the extent and nature of their integration into the health system?

4. METHODS

This protocol has been prepared according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[13]

4.1 Eligibility Criteria for this Review

4.1.1 Types of Studies

A combination of analytical and descriptive studies will be considered for this review. These include randomised controlled trials (RCTs) and controlled clinical trials (CCTs), quasi-experimental, controlled before-and-after studies (CBAs), interrupted time series designs (ITS), cross-sectional studies. “Opinion pieces”, narrative reviews, and letters to the editor will not be included.

4.1.2 Types of Participants

Populations at risk of group A streptococcus infection, rheumatic fever, and/or rheumatic heart disease.

4.1.3 Types of Interventions

Disease prevention or control programmes, defined as a coherent and intentional effort to expand health services to the population.[12] We will use commonly agreed-upon classifications for RHD-related services: primary prevention, secondary prevention, and advanced medical or surgical care. We will focus on the changes in health service delivery brought about by the programme and the downstream impact on intermediate and final health outcomes.

4.1.4 Types of Outcome Measures

Primary outcomes:

- I. Programme characteristics will include: the programme start year, location(s), duration, area of emphasis (services delivered: primary, secondary, tertiary), and inputs.
- II. Programme integration: we will make use of a framework developed by Atun and colleagues to determine the extent of integration into the existing healthsystem.[13]

Integration will be defined as “the extent, pattern, and rate of adoption and eventual assimilation of health interventions into each of the critical functions of a health system”. [13] Six critical health system functions are outlined as: stewardship and governance, financing, planning, service delivery, monitoring and evaluation, and demand generation. [13] In a subsequent review by the same authors, this framework was used to illustrate its use in evaluating the extent of integration for programmes addressing several different health outcomes. [10]

Secondary outcome:

- III. Programme results: A ‘results chain’ framework (**Figure 1**) will be used to identify the effects of various programmes. [15] This is a commonly used tool for evaluating the impact of health programmes. Specifically, the results chain consists of inputs (such as human and physical resources), which produce outputs (such as the volume and scope of services produced), which lead to outcomes (such as changes in behaviours or physiologic indicators of risk), which lead to final impacts (such as reductions in disease-specific incidence and mortality rates).

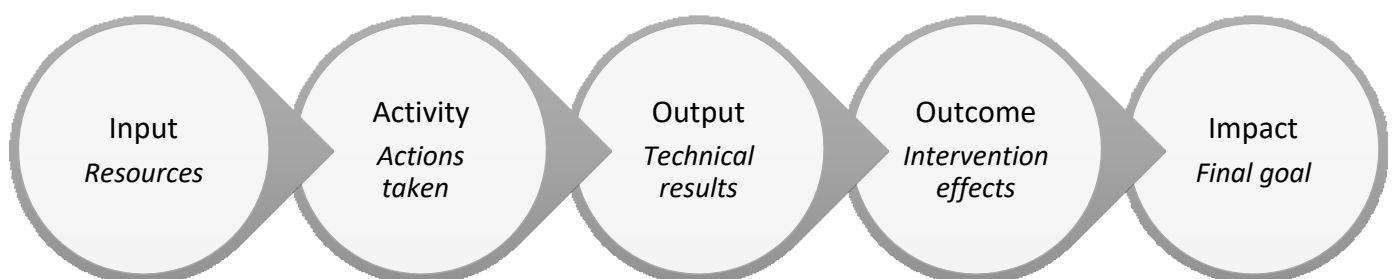


Figure 1: The results chain framework.

4.1.5 Exclusion Criteria

Studies will be excluded should they be published prior to January 1990 or after December 2017, if they do not correspond to the aforementioned study designs, or if they do not display a clear effort to expand health services to people at risk for GAS, ARF, and or RHD.

Studies with insufficient information on programme characteristics will be excluded, as well as studies reporting on fewer than four of the 6 key functions of the health system. Further details on the eligibility criteria are displayed in **Table 1**.

Table 1: Eligibility criteria for this review

	Inclusion	Exclusion
Study Designs	RCTS, CCTs, CBAs, ITS, quasi-experimental, cross-sectional.	Opinion pieces, narrative reviews, letters to the editor.
Study Intervention and Population	A programme showing an intentional effort to expand health services to the population at risk for GAS, ARF, and or RHD.	The intervention is not a health service, and the target population does not include those at risk for GAS, ARF, or RHD.
Programme Characteristics	The start year and duration, the country or region, and the type of service delivered (primary, secondary, tertiary).	Absence of any programme characteristics.
Programme Integration	Information on 4 or more of the 6 critical health system functions.	Information on fewer than 4 of the critical health system functions.

RCT, randomized controlled trial; CCT, controlled clinical trial; ITS, interrupted time series; GAS, group A streptococcus; ARF, acute rheumatic fever; RHD, rheumatic heart disease.

4.2 Search Methods for the Identification of Studies

Electronic databases to be searched include PubMed, Cochrane Central Register of Controlled Trials, Scopus, Web of Science, Africa Wide and CINAHL. Google Scholar and Global Index Medicus (which includes Latin America and the Caribbean database LILACS as well as World Health Organisation Library Information System WHOLIS) will be searched for

grey material. The search will include Medical Subject Headings (MeSh) and free term text items, published in English from the year 1990 onwards (**Table 2**). These restrictions have been chosen since we seek contemporary prevention and treatment programmes with limited time and resources. The reference lists of included papers will be hand searched for relevant studies. Published and unpublished data will be sourced by contacting authors as well as abstracts from the latest by screening abstracts from the latest relevant conferences.

Table 2: Terms used in searching the databases (full search strategy available in Appendix 2).

Subject	Key search terms
#1: Health Service Delivery	Vertical
	Horizontal
	Intergrat*
	Coordinat*
	Co-ordinat*
	Programme*
	Service*
	Health care
	Healthcare
	Delivery of Health Care, Integrated [MeSH]
	Preventative health services [MeSH]
#2: Group A Streptococcus, Rheumatic Fever, Rheumatic Heart Disease	Pharyngitis [MeSH]
	Pharyng*
	Sore throat
	Streptococcus [MeSH]
	Group A strep*
	Rheumatic*
	Rheumatic heart disease[MeSH]
	Rheumatic heart disease
	Rheumatic fever [MeSH]
	Rheumatic fever
	RHD

4.3 Selection of Studies for Inclusion

Two reviewer authors will independently evaluate the titles and abstracts of the search results and decide which papers to include. Clear reasons for exclusion will be documented. Any discrepancies will be discussed and where consensus cannot be reached, resolved with

a third author. The full-text of the articles finalised for inclusion will be retrieved and saved in Mendeley reference manager for further analysis. A flowchart will be presented to summarize the search process and selection of studies for this review, as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

5. DATA EXTRACTION AND MANAGEMENT

Two reviewer authors will independently extract data using the predesigned data extraction form, which will be piloted beforehand with 5 studies to improve its validity (**Appendix 3**).

Data extraction discrepancies will be ameliorated through discussion and where contradictions still remain, a third reviewer will be consulted. Extracted data will include details pertaining to the author, study design, duration and setting, and information for risk of bias assessment. We will extract a variety of qualitative and quantitative data related to our primary and secondary outcomes. Data will be extracted in accordance with our conceptual frameworks – health system key functions, type of services delivered, and results chain. Certain programme results data may not be reported, such as outcomes or impacts. In such cases, this will be noted as unreported during data extraction. Data will be analysed using Review Manager 5.3 (RevMan5) software.

Efforts will be made to contact corresponding authors to source relevant information and clarity regarding missing data. However, if the corresponding authors fail to respond within one week, the other authors(s) will be contacted. The number of studies which do not include data pertaining to our primary and secondary will be noted. Ongoing studies will be classified as such.

6. DATA SYNTHESIS AND MANAGEMENT

This review will synthesise study data using qualitative and quantitative approaches. We will transform programme characteristics into descriptive statistics, such as the proportion of studies focusing on primary prevention. We will create a series of data display matrices, one for each type of clinical service delivered; namely, primary, secondary, or tertiary levels of prevention, or combinations thereof. The matrices will present qualitative and quantitative data along the results chain (columns) for each study (rows) that provide data on the respective programmes. Where appropriate, we will conduct meta-analyses on the change of effect at different points along the results chain, focusing on outcomes (i.e. intermediate clinical outcomes such as the detection of new RHD cases) and impact on population health (i.e. disease incidence, disability, and mortality rates). Care will be taken to pool results only from programmes that have similar models of care delivery; otherwise, we will provide a narrative review of programme outcomes.

Outcome data of included studies will be expressed as a risk ratio with corresponding 95% confidence interval for dichotomous data, or mean difference and standard deviation for continuous data. Where outcomes are measured using different scales, the standardised mean difference will be reported. A random effects meta-analysis will be performed according to the Mantel-Haenszel method in the absence of statistical heterogeneity, methodological difference or high risk of bias. Should the included studies be of substantial heterogeneity and where statistical pooling is not possible, results will be presented in a narrative format, including suitable tables and figures.

Heterogeneity will be evaluated by examining population characteristics, approaches to delivery of interventions, and differences in definitions or measurement of study outcomes. Heterogeneity of the programme effects across studies will be assessed visually by analysing the forest plot, the chi-square test having a 10% level of significance and using the I^2 statistic with cut-offs of 25%, 50% and 75% representing low, medium, and high heterogeneity, respectively.

Our second primary objective, to assess the extent of programme integration into existing health systems, will be represented in the data display matrices using an ordinal scale. If the number of similar studies is sufficient to conduct meta-analyses, we will attempt to identify the influence of programme integration on study outcomes by using either subgroup analysis or random-effects meta-regression with our integration score included as a covariate. Again if data are limited or too heterogeneous to pool, we will summarise our findings in a narrative format.

7. RISK OF BIAS AND QUALITY APPRAISAL

The Critical Appraisal Skills Programme (CASP) checklist will be used to assess the risk of bias of experimental and observational studies included in this review. Information will be gathered on randomization sequence generation, allocation concealment, masking of study participants and personnel, completeness of outcome data, selective outcome reporting and any other sources of bias. The risk of bias assessment will be accompanied by a summary of the reasoning behind the decision. Each included study will be labelled as having low, unclear, or high risk of bias and will be presented in a figure. Any discrepancies of bias assessment will be resolved through discussion or subsequent consultation with a third author.

In order to minimise publication biases, this study will employ strategies to search for, and include unpublished studies such as those found in grey literature. A funnel plot will be used to assess the risk of publication bias which will be critically examined for asymmetry both visually and through the use of formal tests.

Notably, we anticipate finding a variety of descriptive, non-experimental studies. We will extract data relevant to our primary and secondary outcomes above but not attempt to quantify meta-bias in this subset of studies.

The quality of evidence will be assessed using The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Evidence will be graded as very low, low, moderate, or high quality.

8. FUNDING

This research is supported by a scholarship from the National Research Foundation of South Africa.

9. ETHICS

No formal ethical review is required due to the nature of the systematic review which draws on publicly available data.

10. DISSEMINATION

This review will provide evidence regarding efficient models of care and best practice for RHD programmes. A robust analysis of the purpose, extent, and nature of integration for programmes and services will be of interest to decision makers in resource-constrained settings as well as those in more developed regions wishing to scale up RHD-related

activities. This review will initiate the necessary empirical research agenda that will involve prospective studies in a variety of country contexts.

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PART B: LITERATURE REVIEW

1. INTRODUCTION

Rheumatic heart disease (RHD) is a preventable chronic cardiovascular condition which affects more than 30 million individuals worldwide and is responsible for about 300,000 deaths annually.[1] Deaths due to RHD are most prevalent among children and young adults in resource-constrained settings and significantly contribute to global disability and mortality rates.[1] RHD may develop following a single severe episode or multiple episodes of acute rheumatic fever (ARF), an abnormal autoimmune response to untreated Group A streptococcus (GAS) infection.[2]

Prevention of RHD can be achieved through primary prevention of the initial GAS infection or by controlling recurrent attacks of ARF, known as secondary prevention. Intentional efforts to address RHD date back to the 1950s, but appear to have tapered out as improved living conditions and access to penicillin-based treatment largely reduced the burden of RHD in high-income countries (HICs).[3,4] Unfortunately, endemic patterns of RHD remain in low- and middle-income countries (LMICs) and among vulnerable indigenous populations of certain wealthy countries.[1]

In recent years RHD has regained global attention for being a preventable disease, to which the World Heart Federation has responded by setting the goal of a 25% reduction in premature deaths from ARF and RHD among individuals younger than 25 years of age, by the year 2025.[5,6] More recently, the Resolution on Rheumatic Fever and Rheumatic Heart Disease was approved during the 71st World Health Assembly, and in so doing member states are now accountable to show progress toward eradication of the disease.[7] The Addis Ababa Communique followed by the Cairo Accord outline key actionable strategies

eradicate RHD, such as establishing registers, decentralising diagnostic services for ARF and RHD, ensuring a reliable supply of quality benzathine penicillin, implementing a multi-sectoral national RHD programme, and improving access to cardiac surgical services. [8,9]

In order to achieve the desired progress, evidence-based prevention and treatment services require scaling up in the countries and regions which are still heavily burdened with RHD.

Weak infrastructure and limited resources are key barriers to programme implementation

and thus RHD control in LMICs.[2] Integrated care is known for its health system

strengthening features and holistic approach to health care.[10,11] Therefore, an integrated

approach could prove to be useful for the design and implementation of future RHD

prevention and care. By making use of monitoring and evaluation tools, this review will

identify the best practices in RHD care and provide technical assistance for countries

seeking to effectively and efficiently integrate RHD-related health services into existing

health systems.

The scope of this literature review is broad and first describes the pathogenesis, diagnosis

and treatment of GAS, ARF, and RHD. Thereafter, the development of prevention and

control programmes is discussed within the framework of integrated care, providing

context for the concluding discussion.

2. PATHOGENESIS, DIAGNOSIS, AND TREATMENT

2.1 Group A Streptococcus

2.1.1 Properties and Pathogenesis

Streptococcus pyogenes, or group A *Streptococcus* (GAS), is a beta-hemolytic species of

Gram-positive bacteria which mostly affects human pharyngeal or dermal epithelial

cells.[12] The GAS bacterium itself is made up of a cell wall, surrounded by Group A

carbohydrate, protected by a hyaluronic acid capsule (**Figure 1**).[13] M, T, and R surface proteins are extracellular molecules which interact with the hosts' cells.[13] M proteins have been extensively studied since their discovery by Rebecca Lancefield during the early 1900s.[14] More than 200 distinct M protein serotypes have been identified based on the heterogeneous amino N-terminus of the protein.[15,16] This has allowed for the subtyping of GAS strains (*emm*-typing) which has the potential to be targeted in vaccine development.[15]

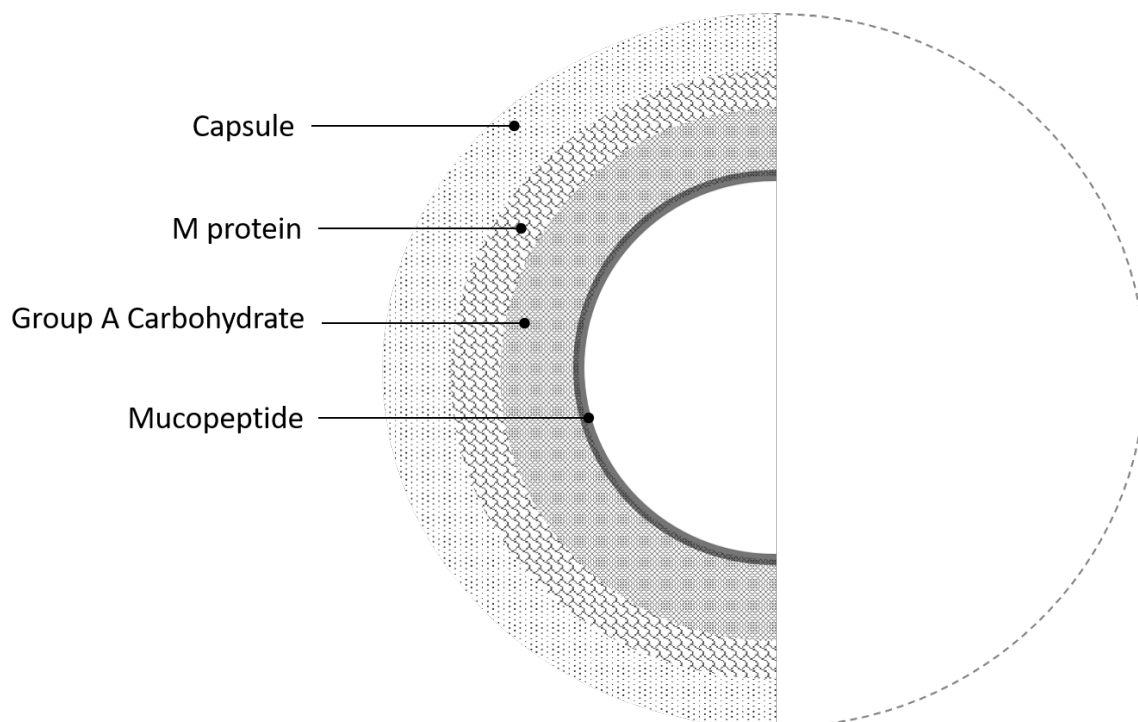


Figure 2: A simplified diagram of a group A streptococcus bacterium. Adapted from [86]

Molecules produced by GAS bacteria, known as virulence factors, act to circumvent the host's natural defences and exploit the inflammatory response, allowing for infection and survival of GAS within the body.[12] Initially, the hyaluronic acid capsule of GAS together with surface M proteins and C5a peptidase enzymes prevent phagocytosis of the bacteria.[17–21] Adhesion molecules anchored to the surface of the bacterial cell allow for

the attachment of GAS to the mucosal layer of the pharynx in a lock-and-key manner.[22] Streptokinase (SK), a potent plasminogen activator secreted by the bacteria, then enables the movement of GAS across normal tissue barriers.[23]

An inflammatory response may follow bacterial infection and colonization, resulting in clinical symptoms of pharyngitis.[13] Alternatively, GAS might remain dormant in the body and the individual will be asymptomatic. Both infected and carrier individuals can transmit GAS to a healthy person via direct contact, such as respiratory droplets, or through contamination of inanimate objects.[24,25] Children have the highest incidence of both respiratory and skin GAS infection.[24,26]

2.1.2 Clinical Features and Diagnosis

Patients with symptomatic GAS pharyngitis infection may present with sudden onset of a sore throat, fever, headache, nausea, patchy tonsillopharyngeal exudates, a scarlatiniform rash, and tonsillopharyngeal inflammation.[27] These symptoms are non-specific and overlap with the clinical features of non-streptococcal pharyngitis.[27]. Therefore, microbiological laboratory testing is required to make a definitive GAS pharyngitis diagnosis.

Culturing throat swab specimens on a sheep blood agar plate (BAP) remains the gold standard for determining whether GAS is present in the pharynx.[28,29] The culturing process requires samples to be stored and transported as soon as possible under specific conditions to the laboratory for incubation of at least 12 hours.[30] In resource-constrained settings, infrequent transport and imperfect storage conditions act as barriers to patient diagnosis and treatment.[31] Most clinicians in LMICs have to diagnose GAS pharyngitis based on patient signs and symptoms alone, for example in Dar es Salaam, Tanzania, where laboratory facilities are absent.[32]

Rapid antigen detection tests (RADTs) offer a faster, point of care diagnosis option. While RADTs seem to solve the obvious diagnostic barriers faced by many LMICs, this tool is expensive and has yet to be validated for these settings.[33] In high-income settings where RADTs are used, throat cultures are still necessary to confirm a negative test due to the varying specificity of the RADT.[27,34]

2.1.3 Treatment

Once diagnosed, treatment with antimicrobial medication is required for 10 days in order to eradicate GAS from the pharynx.[27] A course of oral antibiotics may be prescribed, but intra-muscular administration of benzathine penicillin G (BPG) is preferable.[27] Timely diagnosis and administration of suitable primary prophylaxis (**Table 1**) can prevent acute rheumatic fever (ARF), resolve clinical signs and symptoms, decrease contagiousness and therefore transmission, allowing the patient to return to their regular activities.[27]

Table 1: Infectious Diseases Society of America antibiotic regimens for group A streptococcal pharyngitis.[35]

	Drug	Route	Dose	Duration
Penicillin allergy absent	Penicillin V	Oral	Children: 250 mg twice daily or 3 times daily; adolescents and adults: 250 mg 4 times daily or 500 mg twice daily	10 days
	Amoxicillin	Oral	50 mg/kg once daily (max = 1000 mg); alternate: 25 mg/kg (max = 500 mg) twice daily	10 days
	Benzathine penicillin G	Intramuscular	<27 kg: 600 000 U; ≥27 kg: 1 200 000 U	1 dose
Penicillin allergy present	Cephalexin	Oral	20 mg/kg/dose twice daily (max = 500 mg/dose)	10 days
	Cefadroxil	Oral	30 mg/kg once daily (max = 1 g)	10 days
	Clindamycin	Oral	7 mg/kg/dose 3 times daily (max = 300 mg/dose) 12 mg/kg once daily (max = 500 mg)	10 days
	Azithromycin	Oral	7.5 mg/kg/dose twice daily (max = 250 mg/dose)	5 days
	Clarithromycin	Oral	30 mg/kg once daily (max = 1 g)	10 days

2.2 Acute Rheumatic Fever

2.2.1 Development of Acute Rheumatic Fever

Acute rheumatic fever (ARF) may occur in 0.3-3% of untreated individuals as a delayed sequel to GAS infection following an immune response in the body.[12] GAS-specific antigens are identical to those found in cardiac muscle, synovial tissue or neuronal tissue of the host.[36] This process, known as molecular mimicry, results in an autoimmune response through cross-reacting antibodies.[37,38] Importantly, recurrent ARF episodes are more likely to occur with repetitive GAS infections which are left untreated.[39] While the exact pathogenic mechanisms of ARF are poorly understood, the incurred tissue damage results in the clinical features of ARF.

2.2.2 Clinical Features and Diagnosis

The inflammatory process which implicates the heart, joints, and brain of the host manifests as carditis, arthritis, and Sydenham chorea, respectively.[40] Associated signs and symptoms may include fever, joint pain, involuntary muscle movements and a non-itchy rash.[41] In the absence of a confirmatory biological test, ARF remains a clinical diagnosis. *The Jones Criteria* was first compiled by Dr T Duckett Jones in 1944 and has since undergone several revisions, remaining the global clinical diagnostic gold standard for ARF.[42,43] The latest revision by the American Heart Association released in 2015 has considered more modern epidemiological data on ARF together with the evolution of essential technologies like echocardiography – an ultrasound of the heart.[44] Clinical symptoms are categorised into major and minor criteria for ARF diagnosis according to the population at risk (**Table 2**). In order for an individual to receive a confirmatory diagnosis of initial ARF, they need to present with 2 major manifestations or 1 major and 2 minor, as well as laboratory evidence

for previous GAS infection.[44] For a diagnosis of recurrent ARF, a patient must have a history of GAS infection with 2 major or 1 major and 2 minor or 3 minor criteria.[44] Carditis is heavily implicated in the progression to RHD and remains the most common and severe manifestation of ARF, affecting close to 80% of patients.[45,46] Thus, it is strongly recommended that carditis be assessed by echocardiography in order to establish ARF diagnosis.[44]

Table 2: Summary of the 2015 Jones criteria for diagnosing patients with acute rheumatic fever.[44]

	Low-risk population*	Moderate- and high-risk populations
Major Criteria		
Carditis	Clinical and/or subclinical	Clinical and/or subclinical
Arthritis	Polyarthritis	Monoarthritis, polyarthritis and/or polyarthralgia
Chorea		
Erythema marginatum		
Minor Criteria		
Carditis	Prolonged PR interval, accounting for age variability (unless carditis is a major criterion)	
Arthralgia	Polyarthralgia	Monoarthralgia
Fever	≥38.5°C	≥38°C
Inflammation markers	ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL	ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL

ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

*Low-risk populations are those with ARF incidence ≤2 per 100 000 school-aged children or all-age rheumatic heart disease prevalence of ≤1 per 1000 population per year.

2.2.3 Treatment

Patients experiencing signs and symptoms of ARF require secondary antibiotic prophylaxis in order to return to health and prevent recurrent attacks. This is achieved through regular BPG administration, which can be oral or injected, for at least 10 years following the initial attack.[47] BPG injected intramuscularly is recognised as being more effective than oral doses with a reduction in the reoccurrence of ARF by 87-97%, however there is dispute over

how regular the injections should be given.[48,49] Two- or three-weekly injections are believed to be more effective in preventing ARF reoccurrence [48], but adherence is problematic. Patients from LMICs were found to have better adherence to a 4-weekly regimen compared to a 3-weekly or 2-weekly regimen [50]. Often, the lack of key infrastructure to deliver BPG influences adherence rates. This is demonstrated in New Zealand where patient compliance is reportedly higher among those receiving BPG from local ARF/RHD register programmes compared to primary health care facilities.[51] Importantly, secondary prophylaxis is recognised as being the most cost-effective strategy to control recurrent episodes of ARF and its progression to RHD.[52]

2.3 Rheumatic Heart Disease

2.3.1 Development, Clinical Features and Diagnosis

RHD, a chronic condition, is characterised by lesions to the heart valves which arise as a consequence of prolonged insults to the cardiac tissue during ARF. The mitral and aortic valves (**Figure 2**) are most commonly implicated in RHD, resulting in an abnormal heart sounds and haemodynamic effects.[53] In patients with a known history of ARF, it is assumed that valvular abnormalities represent RHD.[53]

Until the advent of echocardiography, clinicians used a stethoscope to non-invasively listen to heart sounds to diagnose patients suspected of having RHD.[53] The superior sensitivity and specificity of echocardiography has brought to light a truer, more realistic burden of subclinical RHD which was previously underestimated in many regions of the world.[54,55] Recently, the hand-held echocardiogram has gained a lot of attention for its affordability, portable nature, and ease of use. While it lacks the spectral Doppler feature of the standard echocardiogram, the hand-held device is viewed as a promising screening tool for subclinical

RHD, particularly for remote or resource constrained settings.[49,56] A systematic review is currently underway examining the diagnostic accuracy compared to standard echocardiography for the detection of RHD, the results of which are expected to be available soon.[57]

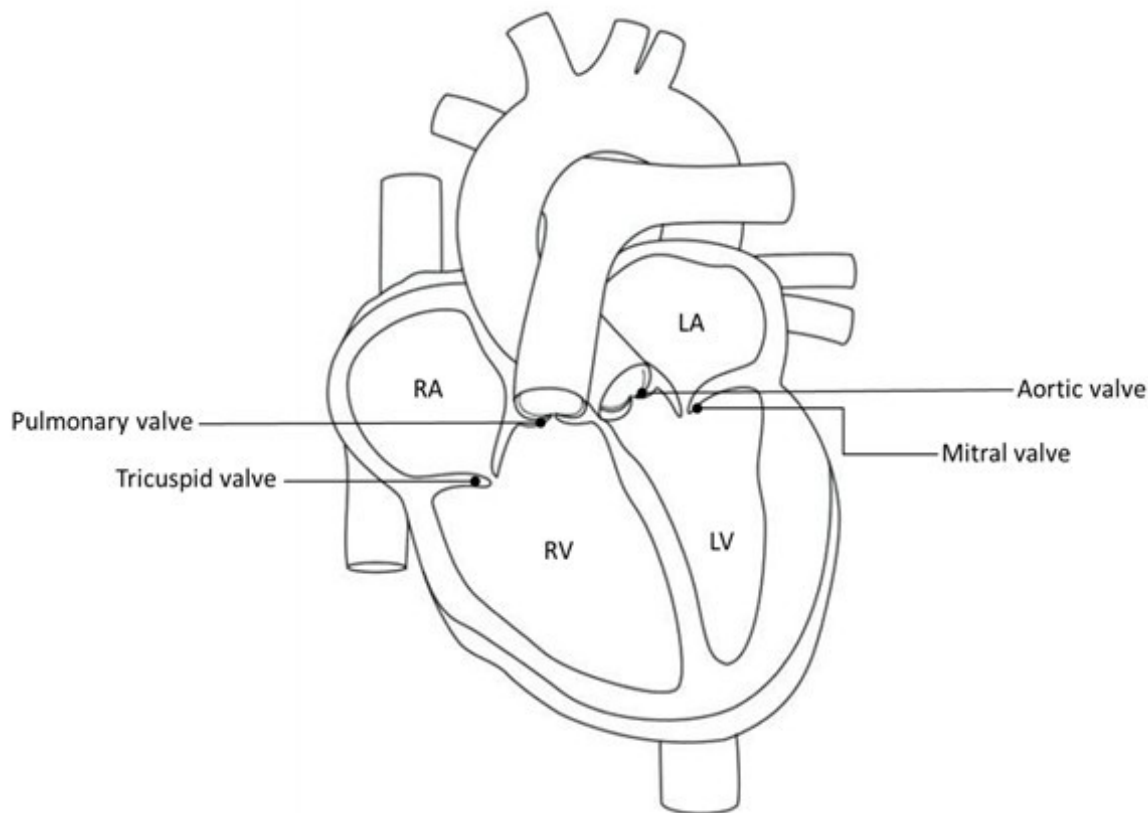


Figure 3: Line drawing showing the chambers and valves of the heart. RA, right atrium; RV, right ventricle; LV, left ventricle; LA, left atrium. Anatomical line drawing downloaded from: <http://getdrawings.com/anatomical-heart-drawing>.

2.3.2 Treatment

Tertiary care involves managing the complications associated with RHD. Often, it is necessary for patients to undergo costly surgery to repair or replace damaged valves of the heart, followed by post-operative care. This is especially the case in developing regions where RHD patients tend to present for care at advanced stages of the disease.[58] Unfortunately, cardiac facilities in LMICs are severely lacking with only 22 cardiac centres for

the estimated 1 billion people residing in sub-Saharan Africa.[59,60] Patients are required to travel cross-country to receive life-saving surgical interventions or rely on humanitarian cardiac teams which visit once or twice a year.[59] Team Heart, a non-governmental organization based in the United States, has been travelling to Rwanda on an annual basis since 2008 to provide care for critical RHD patients.[61] Over the past 10 years, 200 valve implants have been completed by the team.[62]

Following valve replacement, anticoagulants may be prescribed which, if not managed correctly, puts the patient at great risk of thromboembolism or haemorrhage.[63,64] In order to avoid such outcomes, the patient's International Normalised Ratio (INR) needs to be regularly monitored.[65] Quality follow-up and INR facilities are therefore essential for post-operative care of patients. Unfortunately, access to point of care testing is lacking in low resource settings experiencing endemic patterns of RHD.[64] The REMEDY study, a register of RHD patients in 12 African countries, found only 28.3% of RHD patients to be in the therapeutic INR range.[66]

3. ADDRESSING THE BURDEN OF RHEUMATIC HEARTDISEASE

RHD is a preventable condition which disproportionately affects poverty stricken children and young adults living in rural or resource-limited areas.[1] Aside from the desperate need to upscale cardiac surgical services in LMICs, as recently outlined in the Cape Town Declaration,[60] a significant barrier to the control of RHD lies within the implementation of effective primary and secondary prevention in these communities.[67] Therefore, from a health systems perspective, investigation into an effective method of RHD programme implementation is appropriate.

3.1 Programme Design and Implementation

The health care system is viewed as dynamic and complex, with many interdependent interacting components.[68] The implementation of an intervention into a health system is believed to be influenced by a number of key factors such as the nature of the problem, the type of intervention, adoption system, characteristics of the health system, and the overall context in which this all occurs (**Figure 3**).[69] With this considered, health services are typically delivered in a *vertical*, *horizontal*, or *diagonal* manner, each with their own defining characteristics.

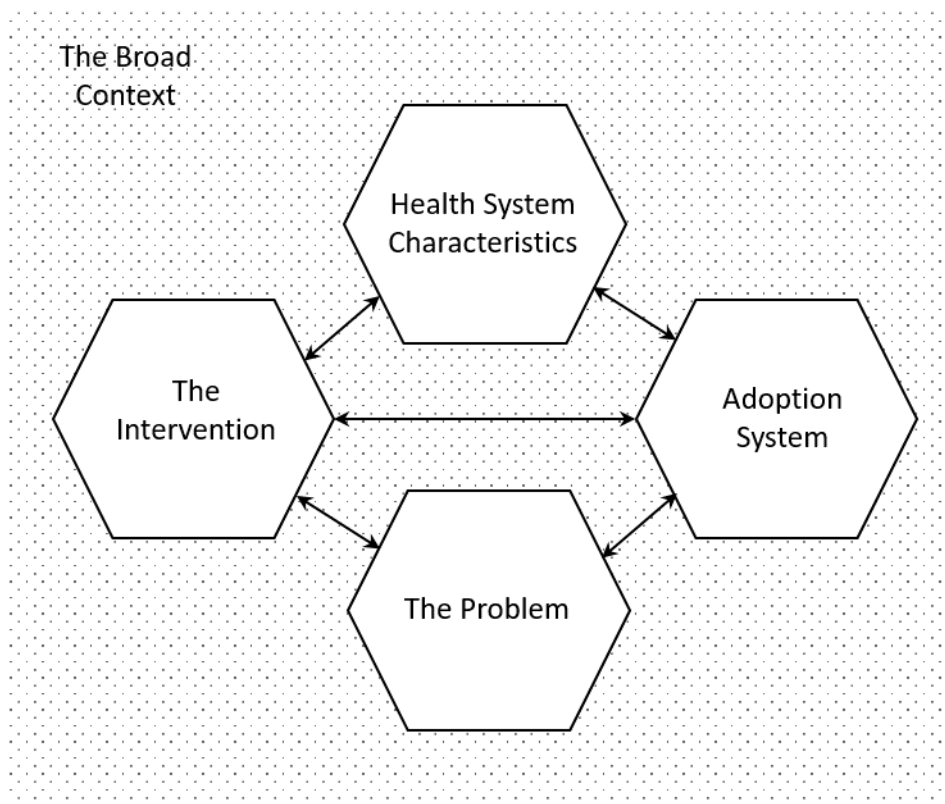


Figure 4: Factors influencing the implementation of a new health intervention. Adapted from [69].

Vertical (non-integrated) programmes are typically disease- or service-specific.[10] They deliver stand-alone services in which dedicated health workers provide care to a targeted population.[10] These types of programmes have been famously effective for the eradication of vaccine-preventable diseases such as smallpox.[70] More recent use of

vertical programmes have been in targeting infectious diseases in middle-income regions such as Latin America and North Africa, however the trade-offs of this type of service delivery involves diverting clinical and human resources away from other diseases and possible interference by international donors.[10,64] For example, in Ethiopia, disease-specific funding thwarted efforts to strengthen the health system.[71,72]

By the horizontal design, more commonly known as *integrated*, services are usually delivered through the national health care system and are commonly believed to be more sustainable, providing a holistic approach to health.[10] Neglected tropical diseases have previously benefited from integrated control programmes, such as schistosomiasis control in Cameroon which simultaneously worked to strengthen the primary health care system.[11] This is in line with the World Health Organization's health system-based definition, which highlights integrated care as "an approach to strengthen people-centred health systems through the promotion of the comprehensive delivery of quality services".[73] However, one must consider that the speed and extent of integrating an intervention is highly influenced by the aforementioned key factors.[69] For example, the ability for a programme to be fully integrated may be limited by context-specific constraints like as financial restrictions on the health system or complex relationships among levels of the government.[69]

There has been a longstanding debate about which of the above two approaches is superior for disease interventions; Atun and colleagues point out that the reality of health care delivery is too complex to confine an intervention to the binary distinction of integrated or not integrated.[69] Realistically, programmes vary in their extent of integration or verticality according to the nuances of the problem being addressed, the proposed solution,

and the context in which this all occurs.[74] The diagonal approach incorporates elements of both vertical and integrated programmes, designed to strengthen primary health care while performing disease specific activities; it has been suggested that a diagonal approach might be well-suited to tackling RHD.[39]

3.2 Integrating RHD control programmes

According to the WHO, a national RHD programme should include primary and secondary activities, health education, training of healthcare providers, epidemiological surveillance, and community involvement.[2] Using elements of integration adds to the sustainability of such a programme as existing health infrastructure is used to cover the primary, secondary, and tertiary levels of care. This is naturally useful for RHD which has its origins in an infectious disease and an autoimmune response, thus intersecting a number of specialities and levels of care.[75]

The WHO first began efforts to address the burden of RF and RHD in 1950s,[3,76] and in 1985 launched the first global programme for the prevention and control of ARF and RHD in 16 developing countries.[77] This was also the first attempt at integrating ARF and RHD care into existing health structures. Secondary prevention efforts included setting up a central register for ARF and RHD patients as well as extensive dissemination of health education to healthcare professionals and the general public.[77] The goal was to reduce the burden of ARF and RHD by creating a comprehensive programme for the local governments to sustain. While the paper indicates that there was a lowered reoccurrence rate of ARF, most countries struggled with basic components required for RHD control, such as the constant provision of penicillin and nearby laboratory facilities.[77,78] The underlying issue was

affordability, and only a few countries expanded the local RHD control efforts beyond the pilot programme.

Cuba was one of the countries which ensued with the WHO's comprehensive RHD control initiative, and is a widely cited example for its successful reduction of the burden of ARF and RHD in the province of Pinar del Rio.[79] The researchers attribute this success to the means of programme implementation, which did not implicate resources outside of the existing healthcare system's capacity.[79] Instead, the primary and secondary prevention programme was funded by Cuba's ministry of health and delivered through local hospitals and primary healthcare facilities.[79] Similarly, a secondary prevention programme was set up in Northern India which made use of existing educational channels to train teachers and healthcare workers, and used local clinics for a registry.[80] The community referral network for suspected ARF and RHD cases resulted in 77 patients being registered over the two year period.[80] The 85-95% secondary prophylaxis compliance was attributed to continued educational efforts, a prophylaxis card dating upcoming injections, and close follow-up of defaulting patients.[80] The number of cases detected in the intervention block increased by four times over the course of the study, whereas there were only 3 additional cases identified in the control block.[80] The intervention and control blocks populations appear to have been exchangeable, which adds to the reliability of the study findings, however no statistical analysis was performed.

A notably successful primary prevention programme was conducted during the 1980s in Costa Rica. The programme focused on improving the diagnosis and treatment of GAS pharyngitis by educating healthcare workers and improving the access to care by increasing the number of peripheral clinics and extending working hours.[81] The standard treatment

regimen was also changed from oral penicillin to intramuscular administration of BPG. These relatively small-scale changes were able to produce a steady decline in the national incidence of rheumatic fever over a five year period.[81] Other primary prevention RHD programmes have been successfully implemented through school systems. In a controlled trial conducted in Southern China, students with a GAS positive throat culture either received school-administered primary prophylaxis straightaway, or were notified to seek care from their regular medical provider.[82] Students receiving prompt sore throat treatment had a significantly lower GAS prevalence compared to that of the control group after a 3 month period.[82]

There is emerging evidence for integrated tertiary care RHD programmes, which are being investigated as a cost-saving and safe means of follow-up care for patients. In 2009, a nurse practitioner (NP) led clinic was established in an ambulatory setting in New Zealand.[83] The aim was to manage and care for patients following valvular heart disease surgery, including the promotion of a healthier lifestyle choices with tailored smoking cessation interventions and referral to diabetes clinics where necessary.[83] RHD patients exhibited a high thromboembolic risk profile, but the NP clinic provided a supportive environment by reinforcing the importance of anticoagulation adherence and maintaining INR targets.[83] More recently in Rwanda, an advanced non-communicable disease (NCD) care programme was embedded into three rural district hospitals as a step toward decentralised follow-up care for RHD patients post-surgery.[84] Patients on anticoagulants were to be seen at least once a month, with transport assistance provided for the lowest income groups.[84] INR was checked during 96% of the visits, and 93% of post-operative patients were receiving penicillin to prevent ARF.[84] By using this model, an impoverished population affected by RHD was provided with close post-operative care. While the NP clinic and decentralised

programmes have yet to be compared to the standard of care, they present alternative models of care for RHD and other valve surgery patients post-operation where care is so obviously lacking.

4. SCOPE OF THIS SYSTEMATIC REVIEW

4.1 A framework for analysis

Integration is a complex concept which is not bound to a single definition. Further, the means of assessing the nature and extent of an integrated programme has been inconsistent. A systematic approach to analysing the integration of RHD programmes is required in order to advise on the success or failure of such an approach for future care.

Atun and colleagues describe a conceptual framework for assessing integration of a targeted health intervention into the health system; they define integration as “the extent, pattern, and rate of adoption and eventual assimilation of health interventions into critical health system functions”. [69] These critical health system functions are: (i) stewardship and governance, (ii) financing, (iii) planning, (iv) service delivery, (v) monitoring and evaluation, and (vi) demand generation. [69] A brief explanation of these functions as well as the criteria for determining the extent of their integration are outlined in **Table 3**. By bringing together certain elements of the health system which affect the adoption, diffusion and assimilation of a health intervention, a macro- and micro-analysis of integration into the health system is made possible. [69] The conceptual framework therefore provides a novel method for the systematic analysis of healthcare programmes which will be used in this study to assess RHD-related care interventions and advise future programme implementation.

Table 3: Criteria for determining the extent of integration for each health system function.[69,74]

	Fully integrated	Partially integrated	Not integrated
Stewardship and Governance <i>Oversight and guidance.</i>	When the governance arrangements for the intervention are the same as those for the general health services or the local or national administrative structures.	The responsibility is shared by the existing general health care system and a specific structure created purposely for the intervention.	When accountability remains exclusively with dedicated specialist entities charged with implementation and management of health interventions, without involvement of the general health care system.
Financing <i>The pooling of financial resources and the provider-payment methods used to allocate these.</i>	Funding is provided entirely through the national or regional general health care budget.	For example, where earmarked funding was provided by the United States Agency for International Development (USAID) but channeled through the PHC system.	When financing is provided directly to an intervention and addressing only a particular disease or problem; or directly funded by an external donor.
Planning <i>Activities, processes and systems for needs assessment, priority setting, and resource allocation.</i>	If the decision-making in relation to the above three areas is undertaken by institutions/stakeholders who are involved in the same tasks for the general health system.	Decision-making responsibility for planning is retained by those managing the health intervention but involves a range of stakeholders (such as civil society representatives, PHC level, or local/regional/national government) through inclusive groupings.	When the decision-making focused solely on the intervention without consideration of general health care activities. This may include specific national government units at national level.
Service delivery <i>Structural and organizational dimensions of the programme.</i>	If their provision is the responsibility of general or multi-purpose health worker.	Where there is shared responsibility for the provision of services between general health workers and the health intervention staff; purpose trained volunteers; when service delivery for a number of interventions is linked.	A number of interventions rely solely on single purpose workers and have no integration with other interventions or general health services.
Monitoring and Evaluation	Use of shared indicators and establishment of integrated data collection, recording, analysis and reporting systems.	When M&E were undertaken jointly by staff from the regional health services and the control programme.	When M&E is undertaken independently by the sponsor, institution, or volunteers of the implementing organisation.
Demand generation <i>The use of appropriate financial incentives and monetary support, insurance, or information, education and communication activities designed to change behaviour.</i>	If mechanisms used to create financial incentives or education and communication activities are provided jointly with the general services or are delivered by primary health care workers.	When education is provided jointly by the targeted programme staff and regional health workers.	Where information campaigns related to health interventions are stand-alone activities, focusing solely on a single problem or disease, and delivered by single-purpose health workers or volunteers.

Integration can occur along more than one dimension (each health system function) and to various extents (fully, partially, or not integrated). In order to assess the effectiveness of a programme, another analytical framework is required: the results chain (**Figure 4**).

Comprising inputs, activities, outputs, outcomes, and impact, the results chain is a causal logic model which is used commonly in monitoring and evaluation to assess the relative impact of an intervention.[85] These types of evaluations are used to inform decision makers, government officials, and other stakeholders about the effectiveness of an intervention. Thus, the results chain is a useful complement for the Atun framework when assessing the evidence for integration of future RHD programmes into health systems.

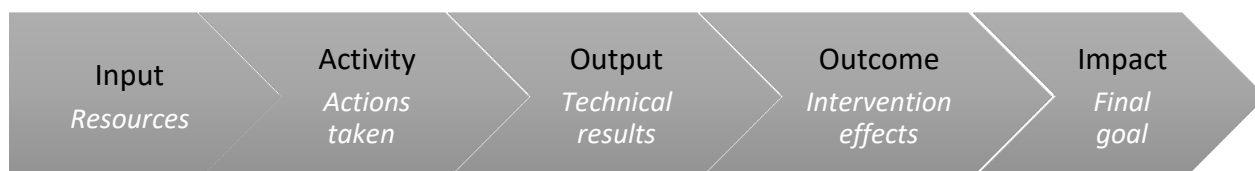


Figure 4: The results chain framework.

4.2 Discussion and potential impact of this work

Atun and colleagues conducted a review to assess the integration of interventions for neglected tropical diseases, nutrition, immunization, child health and development, family planning, and HIV/AIDS.[74] Contrary to the popular notion that health programmes are either vertical or horizontal (integrated), it was found that most programmes were partially integrated, and that the extent of integration varied across each of the six critical health system functions.[74] It was strongly argued that such heterogeneity was desirable given differences in health system design, capacity, and priorities.[74] For some programmes, such as child immunization, targeted campaigns may actually be more effective, efficient,

and sustainable. For other programmes, such as those that provide clinical care for diabetes and other complex chronic diseases, episodic community-based activities are unlikely to achieve significant health impact or be financially sustainable, and integrated approaches delivered at primary health centres are needed.[74]

Amongst non-communicable diseases, RHD and its antecedents represent a unique set of considerations that span a wide spectrum of health system activities. Some aspects of RHD prevention have much in common with infectious disease control. For example, surveillance and notification policies are needed in order to identify and respond quickly to ARF outbreaks and ramp up primary prevention activities. Other aspects – such as secondary prevention – have more in common with clinic-based care for hypertension, diabetes, and HIV/AIDS. The frequent need for (highly-effective) tertiary surgical and medical care also creates additional complexity. In light of all this, there is unlikely to be a “one size fits all” approach to RHD prevention and control in LMICs. What is needed, which this systematic review will begin to provide, is evidence regarding efficient models of care and best practice. A robust analysis of the purpose, extent, and nature of integration for programmes and services will be of interest to decision makers in resource-constrained settings as well as those in more developed regions wishing to scale up RHD-related activities. We anticipate that this review will raise more questions than propose solutions and view this as a first step in an empirical research agenda that will involve prospective studies in a variety of country contexts.

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ABSTRACT

Background: Rheumatic heart disease (RHD), a sequel of group A streptococcal pharyngitis, is a significant cause of premature deaths, primarily in poverty-stricken communities and countries. Following on a 2018 World Health Assembly resolution on RHD, there is increasing need for evidence to guide the implementation of successful RHD programmes that are integrated into national health systems.

Objectives: To assess the effectiveness of programmes targeting RHD prevention and control according to the extent and nature of integration into the health system.

Methods: A comprehensive literature search was performed among electronic databases and grey literature, complemented by hand searching reference lists, to identify analytical and descriptive studies reporting on prevention and control programmes for populations at risk for GAS pharyngitis, acute rheumatic fever, and/or RHD. Studies needed to be published in English between 1 January 1990 and 31 December 2017. RHD programme integration was analysed according to a previously described framework, and programme effectiveness data were extracted and analysed using a results chain framework. A meta-analysis was performed on secondary prophylaxis adherence. Bias was assessed using the Critical Appraisal Skills Programme checklist. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

PROSPERO registration number: CRD42017076307

Results: Six-hundred and fifty-eight publications were identified. Data were extracted from five observational studies meeting with the inclusion criteria. Studies were similar in extent and nature (health system function) of integration; none of the programmes were completely integrated or non-integrated. One study reported on the impact of the programme. Secondary prophylaxis adherence improved among partially integrated RHD programmes (RR, 1.18 [95% CI, 1.03 to 1.36], 3 studies, n=618). In terms of quality appraisal, risk of bias was low in two studies, and indeterminable in the remaining three studies.

Conclusions: There is evidence that partially integrated RHD programmes are beneficial for a number of study outcomes. This review provides a starting point for the design and implementation of future RHD programmes by outlining current best practice for integration and identifying the key gaps in knowledge.

Keywords: Group A streptococcus, Rheumatic Fever, Rheumatic Heart Disease, Integrated Care, Prevention and Control.

Strengths and Limitations

- This is the first systematic review to analyse the integration of prevention and control programmes for rheumatic heart disease.
- The use of multiple complementary conceptual frameworks (health system critical functions, type of services delivered, and results chain) provides a unique and comprehensive assessment of each programme.
- We recognise that restricting the search to English may have introduced language and publication bias, and that the time period restriction would have excluded older studies with important historical information and experience, predominately from high-income countries.

1. INTRODUCTION

Rheumatic heart disease (RHD) is a potentially fatal yet preventable condition which begins with a sore throat and results in damage to the valves of the heart. RHD is responsible for about 300,000 deaths annually, most of which are children and young adults from resource-constrained settings.[1] Crowded and unsanitary living conditions enable the spread of group A streptococcus (GAS), the infectious agent inducing an autoimmune response, resulting in the progression from pharyngitis to acute rheumatic fever (ARF).[2] Under- recognition of ARF coupled with inadequate access to medical care often results in RHD and sometimes premature death among these patients.[2]

Strategies to combat disease progression include penicillin primary prophylaxis following GAS diagnosis, or secondary prophylaxis for patients diagnosed with ARF.[2,3] In patients who present for medical attention late in the disease, heart valve surgery is required to repair the damage caused by severe or recurrent episodes of ARF, often followed by a lifelong dependence on anticoagulants and penicillin.[4] In countries with endemic patterns of RHD, weak infrastructure and limited resources are key barriers to RHD prevention and control efforts.[5]

RHD has been placed on the international agenda, with the World Heart Federation setting out to achieve a 25% reduction in premature deaths from ARF and RHD among individuals younger than 25 years of age, by the year 2025.[6,7] More recently, the World Health Assembly approved the Resolution on Rheumatic Fever and Rheumatic Heart Disease thereby committing countries to showing progress in the eradication of RHD.[8] The Addis Ababa Communique and Cairo Accord provide key actionable strategies to eradicate RHD which includes implementing a multi-sectoral national RHD programme.[9,10]

In order to achieve the desired progress, evidence-based prevention and treatment services require scaling up in the countries and regions which are still heavily burdened with RHD. A possible solution is to design comprehensive prevention and control programmes which are integrated into the respective country's health system, as integrated care has been found to have health system strengthening features.[11,12] Thus far, RHD programmes have been evaluated using uncontrolled approaches, and there is little evidence on how to efficiently integrate RHD-specific activities into broader health systems.

This systematic review sought to examine previously published reports of RHD prevention and control programmes in order to determine the nature and extent of integration, and how this integration (or lack thereof) might affect programme success. In doing so, this research will synthesise existing evidence and identify additional research that is needed to guide the implementation of future RHD programmes.

2. METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed in this systematic review (**Appendix 1**). This review protocol has been published in the PROSPERO International Prospective Register of systematic reviews (<http://www.crd.york.ac.uk/PROSPERO>), registration number CRD42017076307.

2.1 Search Strategy

A comprehensive search strategy (**Appendix 2**) was used to find studies published in PubMed, Cochrane Central Register of Controlled Trials, Scopus, ISI Web of Science, Africa Wide and CINAHL. Google Scholar and Global Index Medicus (which includes Latin America and the Caribbean database LILACS, as well as World Health Organisation Library Information System (WHOLIS)) were searched for grey literature using key search terms. The

reference lists of relevant studies were hand searched to further identify possible articles.

Studies were eligible for screening if they were published in English between 1 January 1990 and 31 December 2017.

2.2 Study Selection

After removing duplicate publications, two authors independently screened titles and abstracts. Discrepancies were resolved by discussion, after which two reviewers (JA and DW) independently scrutinised the full text articles to determine inclusion. Studies were included if they reported on a health programme (defined as an intentional effort to expand health services) directed at populations at risk for group A streptococcus infection, rheumatic fever, and/or rheumatic heart disease. In addition, studies were included if they had information on programme characteristics such as the duration and location of the programme, the type of services delivered, and the programme inputs, as well as sufficient details on at least four of the six key functions of the health system, namely: (i) governance, (ii) financing, (iii) planning, (iv) service delivery, (v) monitoring and evaluation, and (vi) demand generation. Randomised controlled trials (RCTs), controlled clinical trials (CCTs), quasi-experimental, controlled before-and-after studies (CBAs), interrupted time series (ITS), or cross-sectional designs were included. “Opinion pieces”, narrative reviews, and letters to the editor were excluded.

2.3 Data Extraction and Analysis

The data extraction form was piloted using five publications (**Appendix 3**). Data were subsequently extracted by JA and checked by DW. A consensus was reached on any discrepancies.

For each publication, the programme characteristics, extent of integration, and programme results were extracted. Programme characteristics included basic data such as target population, scale, and duration, as well as detailed data on inputs organised into the six “building blocks” used in the WHO health systems framework. The extent of integration was characterised for each of the six key functions of the health system and assigned a score from 1 to 3 depending on whether the programme was not integrated, partially integrated, or fully integrated (or not reported). Integration scores for each of the six key functions were summed to a composite score with a maximum value of 18. **Appendix 4** provides further details on how the extent of integration was scored. A results chain comprising programme inputs, activities, outputs, outcomes, and impacts, was populated for each study using the extracted data. A meta-analysis of study outcomes was performed using Review Manager 5.3.[13] Data were either pooled or presented without totals depending on the type of outcome.

The first six domains of the Critical Appraisal Skills Programme (CASP) checklist were used to assess the risk of bias of the included studies.[14] Domains were scored as ‘Y’ (bias absent), ‘N’ (bias present), not applicable, or unclear.

3. RESULTS

The search identified 658 publications, of which 94 were duplicates, leaving a total of 564.

An additional seven articles were found following grey literature and reference list searches.

During title and abstract screening, 537 studies were excluded. The remaining 34

publications underwent detailed assessment; a further 29 articles were excluded, mostly

because of unacceptable study design or insufficient information on programme integration

(Figure 1). Five articles were included in this systematic review.

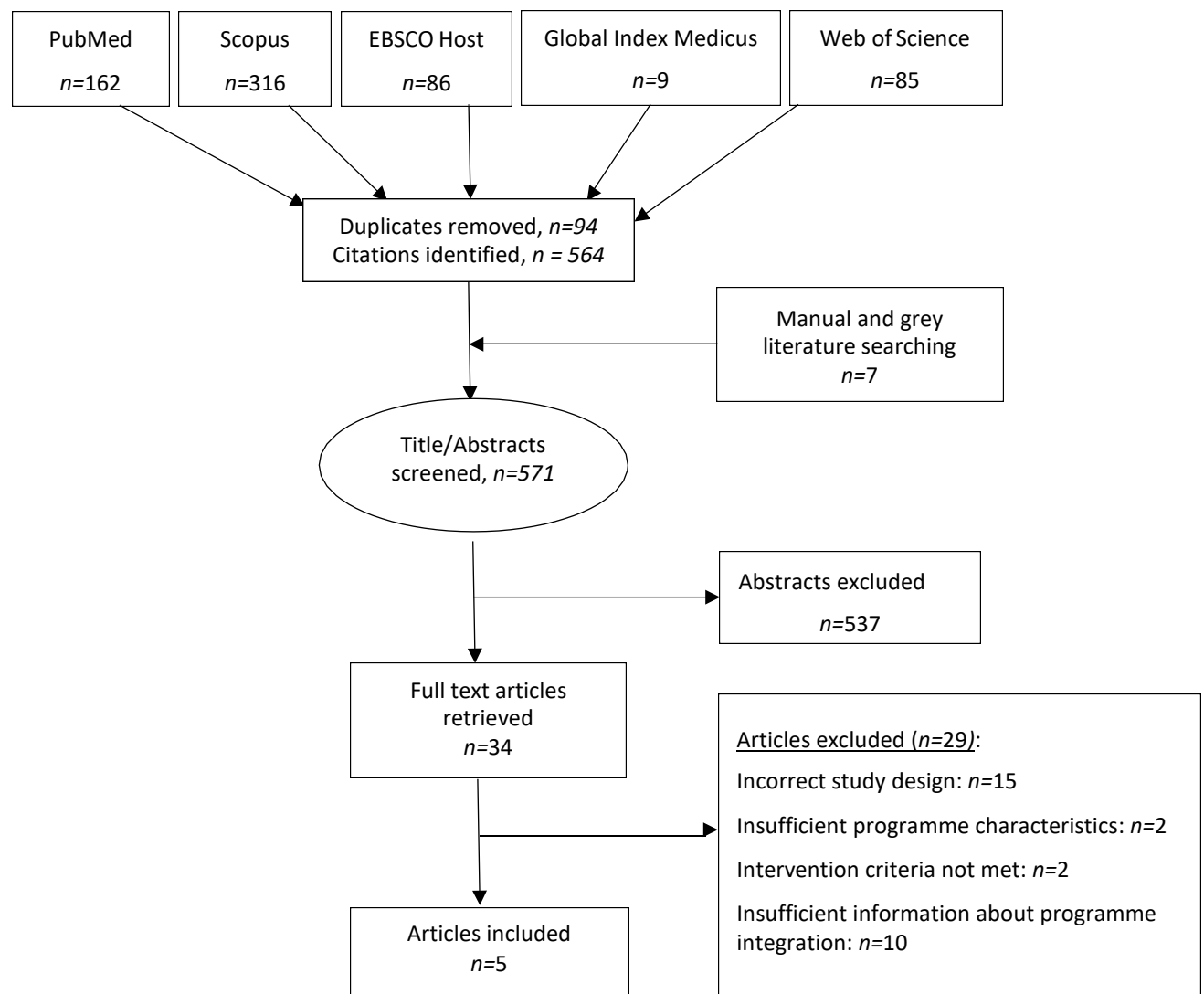


Figure 5: Flow diagram of the search process and selection of eligible publications for the systematic review.

3.1 Study Characteristics

Table 1 provides summary characteristics of the five studies included in this systematic review. All of the studies were observational; three used a cross-sectional design while the remaining two used a quasi-experimental (before and after) study design. Four of the five studies focused on secondary prevention of RHD,[15–18] though one also had a primary prevention component.[16] A single study targeted tertiary care.[19]

The outcomes measured varied across the studies with none of the studies specifically assessing approaches to integrating RHD care as a primary study objective. A variety of geographical locations were covered by the included studies, targeting at-risk communities in Africa, the Americas, South-East Asia, the Eastern Mediterranean, and the Western Pacific region. The shortest study duration was two years while the longest study continued for 10 years.

Table 1: Summary of characteristics of included studies (ordered chronologically)

Study ID	Country and region	Programme duration	Description of the intervention	Study outcome(s) measured	Level(s) of prevention or care			Programme scale: numbers of healthcare workers and patients involved
					1°	2°	3°	
Iyengar 1991[15]	India: Haryana State, Ambala district.	2 years	An ARF/RHD health education and training programme for health workers, teachers, and school pupils, as well as the registration of new cases and prescription of penicillin.	I. The number and source of: suspected case referrals, registered cases, and confirmed cases of RF and RHD (case detection rate) II. Adherence to secondary prophylaxis.		✓		202 healthcare workers and 773 teachers were trained to recognise the signs and symptoms of ARF and RHD. Of the 254 suspected case referrals, 77 were registered in health centres, of which 61 were confirmed and began secondary prophylaxis.
WHO 1992[17]	16 countries participated: (Africa) Mali, Zambia, Zimbabwe; (Americas) Bolivia, El Salvador, Jamaica; (Eastern Mediterranean) Egypt, Iraq, Pakistan and Sudan; (South-East Asia) India, Sri Lanka and Thailand; (Western pacific) China, the Philippines and Tonga.	4 years	Personnel training, health education and a central ARF/RHD register.	I. Secondary prophylaxis coverage. II. ARF reoccurrence.		✓		Across all of the countries, 24 398 personnel trained; 33 651 patients were registered.
Nordet 2008[16]	Cuba: Pinar del Rio.	10 years	A community based prevention and treatment of ARF/RHD through healthcare education and training of health personnel as well as	I. The incidence of ARF (new and recurrent cases). II. The prevalence and severity of RHD.	✓	✓		All 5 – 25 year old permanent residents of the province during the study period were included (n = 273 933).

			the establishment of dedicated register centres.	III. Secondary prophylaxis compliance. IV. The proportion of patients requiring hospitalization.		
Ralph 2013[18]	Australia: Northern Territory.	3 years	A continuous quality improvement (CQI) strategy to improve the documentation and care of ARF/RHD patients.	I. Proportion of patients receiving scheduled BPG. II. Proportion of patients reviewed by their doctor in the past two years. III. The quality of data recorded on ARF/RHD patients: ARF episodes and RHD risk category information.	✓	6 health centres participated; 154 ARF/RHD patients.
Kwan 2013[19]	Rwanda: Kirehe and Southern Kayonza districts.	4.4 years	Outpatient heart failure services implemented at pre-existing integrated NCD clinics at two rural hospitals. Portable ECG and algorithms were used for the diagnosis and management of patients with suspected heart failure.	I. Distribution of conditions (including RHD) among heart failure patients. II. Programme retention. III. Mortality among patients with confirmed diagnoses.	✓	Each clinic team included 2 nurses and 2 administrative personnel, supervised by generalist physicians. Out of 237 patients suspected of heart failure, 192 had a confirmed cardiologist diagnosis and were enrolled in the heart failure programme.

ARF, acute rheumatic fever; RHD, rheumatic heart disease

3.2 Models of Care: Inputs and Activities

Iyengar and colleagues implemented a secondary prevention programme in Northern India, which was financed by a grant from the WHO Arab Gulf programme for development (AGFUND).[15] The programme included 202 healthcare workers and 773 teachers (in 147 schools), who were trained to recognise suspected cases of ARF and RHD. Educational materials in the form of posters, pamphlets and heart models further delivered information about ARF and how to seek treatment. Through this community-based referral system, suspected cases of ARF and RHD could be sent to the nearest health center for diagnosis and treatment. Standard diagnostics for ARF and RHD were used. A rural health centre-based registry was set up where penicillin injections were administered by pharmacists or nurses. Each registered patient received a secondary prophylaxis card and could receive treatment at any of the four health centres in the area.

The World Health Organization initiated a secondary prevention pilot programme in sixteen different countries.[17] The Ministry of Health in each country was responsible for the operationalisation of the programme, with external funding assistance provided by the AGFUND. Each country employed a national programme manager and a multi-disciplinary advisory committee. A total of 2 138 doctors, 16 480 school teachers, and 5 780 other health personnel received training on ARF and RHD. Group sessions were available for the general public. Further education was disseminated by pamphlets, brochures, posters, radio and television. A central ARF/RHD register was set up in each country to manage patients and deliver secondary prophylaxis through the primary health care system. Guidelines and protocols for care delivery were based on the 1988 WHO Technical Report Series. Case finding efforts focused on the screening of schoolchildren, hospital retrospective case

surveys, and referral of suspected or confirmed ARF/RHD cases from hospitals, private clinics or other sources.

Nordet and colleagues report on a 10-year effort to roll out primary and secondary prevention in one province in Cuba (273 933 individuals aged 5-25 in the province were included).[16] The programme was organized and administered by an advisory committee that was part of the provincial health office. Clinical services and educational materials provided as part of the programme were funded through the Ministry of Health and delivered in local hospitals and primary healthcare facilities. Standard medications and diagnostics for pharyngitis, ARF, and RHD were employed. Health information was managed mainly by means of dedicated ARF registers at the provincial teaching hospital and 6 local hospitals. The study did not provide detailed information on systems of (clinical) care delivery but did describe novel healthcare worker and public education campaigns which were intended to increase demand for primary and secondary prevention services.

Ralph and colleagues conducted a secondary prevention programme to promote the implementation of national ARF and RHD management guidelines in Australia.[18] Six primary health care clinics in Aboriginal communities of the Northern Territory (NT) region took part. A project management committee was established comprising the lead project investigators, health service managers, clinicians, staff of the NT RHD Control Program, and staff of RHD Australia. The 3-year project was financed by The National Heart Foundation of Australia, UNICEF Australia Health and the NT Department of Health and Community Services. A continuous quality improvement (CQI) intervention was implemented at the clinics to facilitate the use of the national best-practice ARF/RHD guidelines. The CQI method included two essential components: an RHD clinical audit tool for data collection

from clinical records, and the ABCD Systems Assessment Tool (SAT) to assess the clinic systems through discussions with health centre staff about the strengths and weaknesses of their health centre. The CQI was continually revised and improved and annual assessment of ARF/RHD health services were performed.

Kwan and colleagues performed a cross-sectional analysis on a tertiary care programme.[19] The heart failure programme was embedded into existing non-communicable disease (NCD) clinics of two rural hospitals in Rwanda and was supported by Rwanda's Ministry of Health as well as the non-governmental organisation Partners in Health. The government-subsidised health insurance covered services and medication with modest co-payments charged to individual patients. Further funding from Partners in Health protected patients from health care related out-of-pocket expenses and provided a transportation allowance. One day per week was dedicated to heart failure patient care at the NCD clinics. Each clinic team included 2 nurses and 2 administrative personnel, supervised by generalist physicians. Nurses underwent specialised training on ECG and algorithms for the diagnosis and management of heart failure. The cause of heart failure was determined following a physical examination and basic echocardiography; diagnosis was guided by pre-defined criteria. Following a diagnosis, each patient would receive a therapeutic plan, 6-week follow ups by nurses, and social support if necessary. Medication was administered daily and directly observed by a community health worker to ensure compliance. The exact diagnostic guideline used for RHD was unclear, but patients were treated with penicillin prophylaxis.

3.3 Extent of Integration

Table 2 describes the extent (fully, partially, not, unknown) and nature (type of health system function) of integration for the RHD prevention and control programmes included in

this study. The composite programme integration score was similar across all of the studies (either 9 or 10 out of 18), meaning that none of the programmes were completely integrated into the health system across all key functions.

Financing was most often partially, if not fully, integrated across all of the programmes. Funds which did not come from the general health budget were supplemented by external organisations (such as AGFUND) but were channeled through the health system. Service delivery and demand generation were the second most integrated health system functions. The service delivery model employed by primary and secondary programmes were similar, where prophylaxis was administered in primary health care settings together with other health services, while case-finding efforts were more targeted. Similarly, demand generation was often executed separate from other health education activities (i.e., dedicated campaigns on RHD) but undertaken as part of the local government activities.

Stewardship and governance was either partially or not integrated. Ministries of Health contributed to the governance of several programmes, but often accountability lay solely with a dedicated entity (either within the ministry or within an academic medical institution). Programme planning and monitoring and evaluation were almost never integrated into the health system among these programmes. Public health sector employees were usually involved in planning, but decision-making appeared to focus on RHD alone and did not consider other aspects of the health system or other diseases. There were insufficient details about stewardship and governance and programme planning for the Rwandan tertiary care intervention. Monitoring and evaluation was not well described in the primary and secondary programme implemented in Cuba.

Table 2: The extent and nature of integration by level of prevention for rheumatic heart disease programmes in various countries.

	Critical health system function						Total integration score (/18)
	Stewardship & Governance	Financing	Planning	Service delivery	Monitoring & Evaluation	Demand generation	
Primary Prevention							
Cuba (Nordet 2008)[16]							10
Secondary Prevention							
Australia (Ralph 2013)[18]							10
Cuba (Nordet 2008)[16]							10
India (Iyengar 1991)[15]							9
Multiple countries (WHO 1992)[17]							10
Tertiary care							
Rwanda (Kwan 2013)[19]							9
Key							
Fully integrated		Partially integrated					
Not integrated		Unknown					

3.4 Programme Performance: Outputs, Outcomes and Impact

Each study reported on slightly different programme outcomes; only the Cuban study presented evidence of the impact of their programme on disease endpoints (incidence, prevalence, and mortality) (**Table 3**). The primary and secondary programmes in Cuba resulted in fewer recurrent and first ARF attacks, and there was an overall decline in the prevalence of ARF and RHD. The severity of RHD was also controlled with fewer patients requiring hospitalization.[16] In Australia's Northern Territory, there was a statistically significant improvement in the details documented on ARF and RHD patients, but the overall proportion of patients receiving $\geq 80\%$ of scheduled BPG did not improve.[18] The programme in India successfully improved the ARF and RHD case detection rate in a high-risk community (from 7.8 cases per 100 000/year to 27.5 cases per 100 000/year), and registered patients maintained an 85-95% secondary prophylaxis compliance.[15] The average rate of prophylaxis coverage was 70% in the RHD programme implemented by WHO in multiple countries.[17] The tertiary care clinic in Rwanda saw 61 patients with RHD, of which 3 died, over the course of 4.4 years.[19]

Table 3: Programme performance

Country (Study ID)	Outputs	Outcomes	Impact
Primary prevention			
Cuba (Nordet 2008)[16]	<ul style="list-style-type: none"> Increased medical awareness among young patients. 	<ul style="list-style-type: none"> Timely diagnosis and treatment of strep-throats. 	<ul style="list-style-type: none"> The incidence of first ARF attacks declined from 12.2 per 100 000 in 1986 to 2.1 per 100 000 in 1996.
Secondary prevention			
Australia (Ralph 2013)[18]	<ul style="list-style-type: none"> The number of clinical records audited each year were 154 in 2008, 145 in 2009, and 156 in 2010. 	<ul style="list-style-type: none"> The proportion of patients receiving BPG increased from 81/116 (70%) at baseline to 84/103 (82%) in year three, $p = 0.04$. The proportion of people receiving $\geq 80\%$ of scheduled BPG did not improve, remaining around 25% across all six health centres over the study duration. More patients were reviewed by their doctor within the past two years: from, 112/154 (73%) to 134/156 (86%), $p = 0.003$. Improved details on patients with ARF/RHD: ARF episode documentation increased from 31/55 (56%) to 50/62 (81%) ($p=0.004$), and RHD risk category documentation from 87/154 (56%) to 103/145 (76%) ($p < 0.001$). Patients within the recommended INR range increased from 64% to 75%. 	<ul style="list-style-type: none"> <i>Not reported</i>
Cuba (Nordet 2008)[16]	<ul style="list-style-type: none"> 327 patients registered over the study period. 	<ul style="list-style-type: none"> Increased regular secondary prophylaxis compliance of registered patents (from 50% in 1986 to 93.8% in 1996). 86.1% decline in the cost of managing the disease. 	<ul style="list-style-type: none"> Decline in the prevalence of ARF and RHD (8.0 to 2.0 cases per 1 000 schoolchildren). Decline in the incidence of recurrent attacks of ARF (6.4 to 0.4 per 100 000). Decreased severity of RHD (5 cases of severe RHD in 1986 to only 1 in 1996) Decrease in the number and of patients requiring hospitalization after the acute attack (from 41.1% of the 134 registered

			cases during 1986-90 to 8.3% of the 193 registered cases during 1991-96).
India (Iyengar 1991)[15]	<ul style="list-style-type: none"> ▪ A total of 254 suspected cases of ARF or RHD referred by teachers, health workers, and medical officers. ▪ The diagnosis and registration of 77 new cases of ARF/RHD (of which 61 were subsequently confirmed to have the disease). 	<ul style="list-style-type: none"> ▪ 3.5 time increases in the case detection rate in the intervention block (7.8/100 000/year to 27.5/100 000/year). ▪ 95% compliance to secondary prophylaxis in the first 6 months, this declined to 85% after 2 years. 	<ul style="list-style-type: none"> ▪ <i>Not reported</i>
Multiple countries (WHO 1992)[17]	<ul style="list-style-type: none"> ▪ 33 651 total patients identified and registered. ▪ 95.7% of patients received BPG injections, 2.1% oral penicillin, 0.1% sulfadiazine, and 2.1% erythromycin. ▪ 36 patients had an adverse reaction to BPG (0.3% patient-years), of whom 4 died. 	<ul style="list-style-type: none"> ▪ The rate of average prophylaxis coverage was 70%. ▪ The rate of coverage per 100 patients registered per month averaged 63.2% (range, 23.8-96.9%). ▪ Reoccurrence of ARF occurred in 53 patients (0.4% patient-years), of whom only 2 were receiving regular BPG. 	<ul style="list-style-type: none"> ▪ <i>Although it is stated that the reoccurrence rate of ARF decreased, no evidence was presented.</i>
Tertiary care			
Rwanda (Kwan 2013)[19]	<ul style="list-style-type: none"> ▪ 192 patients were confirmed to have heart failure and were enrolled at the clinic. Of this cohort, 61 patients (32%) had RHD (26 patients were below the age of 18 years and 35 patients were adults). ▪ Over the course of 4.4 years, the mean time spent in care was 19 months. The median time in care for alive patients with complete records (n=169) was 13 months for children and 20 months for adults. 	<ul style="list-style-type: none"> ▪ The observed retention in the programme was 62%. Fifty-five patients (29%) were lost to follow-up. ▪ 18 patients (9%) died, of which 3 had RHD. Mortality might be underestimated due to those lost to follow-up. 	<ul style="list-style-type: none"> ▪ <i>Not reported</i>

3.5 Quantitative Analysis

3.5.1 Acute Rheumatic Fever and Rheumatic Heart Disease-Related Outcomes

Overall, programmes that are at least partially integrated in several dimensions appear to have a positive effect on clinical outcomes (**Figure 2A**). Specifically, improvements in the following outcomes were documented: incidence of first ARF attacks (RR, 0.08 [95% CI, 0.02 to 0.33]), recurrent ARF attacks (RR, 0.22 [95% CI, 0.07 to 0.76]), hospitalization rates following an acute AFR attack (RR, 0.22 [95% CI, 0.00 to 0.15]), rates of severe RHD (RR, 0.05 [95% CI, 0.01 to 0.45]), prevalence of ARF and RHD (RR, 0.24 [95% CI, 0.16 to 0.36]), and patients out of INR range (RR, 0.70 [95% CI, 0.23 to 2.11]). All of the outcomes were statistically significant, except for patients out of INR range which contains the null value of one in the 95% confidence interval.

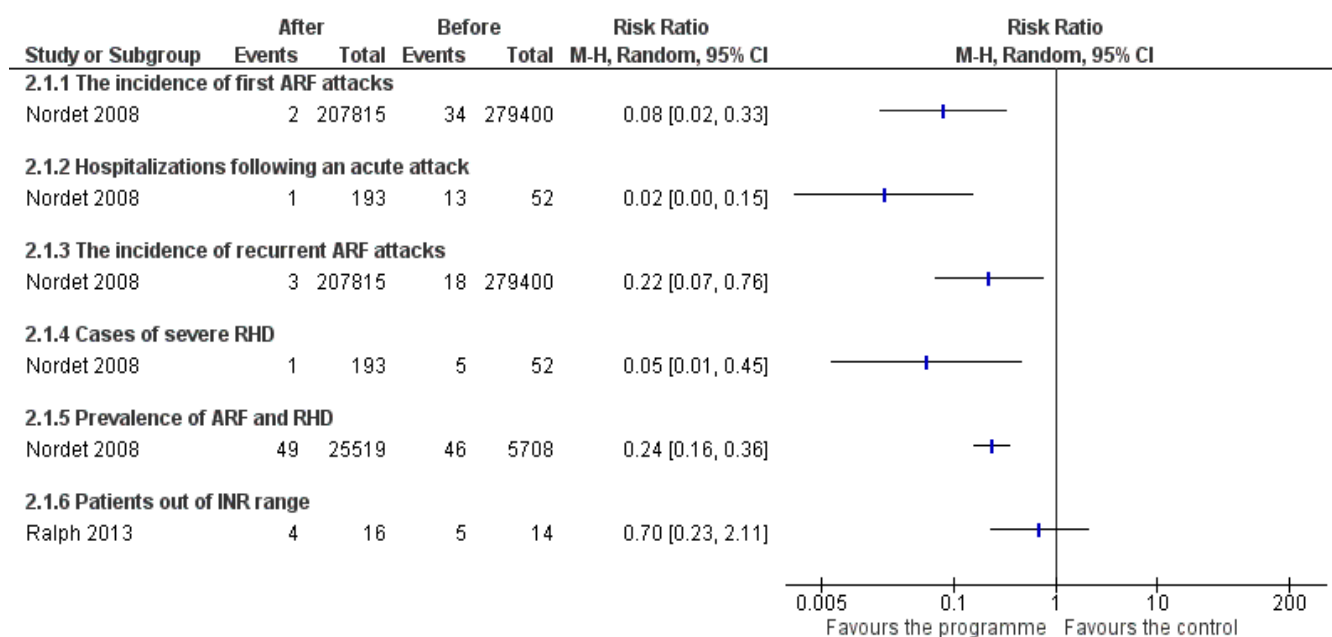


Figure 2A: The effect of an integrated AFR/RHD programme on ARF/RHD-related outcomes.

3.5.2 Acute Rheumatic Fever Secondary Prophylaxis Compliance

Data on secondary prophylaxis were amenable to meta-analysis. Secondary prophylaxis compliance was defined in three studies as the probability of a patient receiving $\geq 80\%$ of administered prophylaxis on a regular basis. There was a significant improvement in secondary prophylaxis compliance (RR, 1.18 [95% CI, 1.03 to 1.36], 3 studies, n=618) amongst patients subjected to a partially integrated programme (**Figure 2B**).

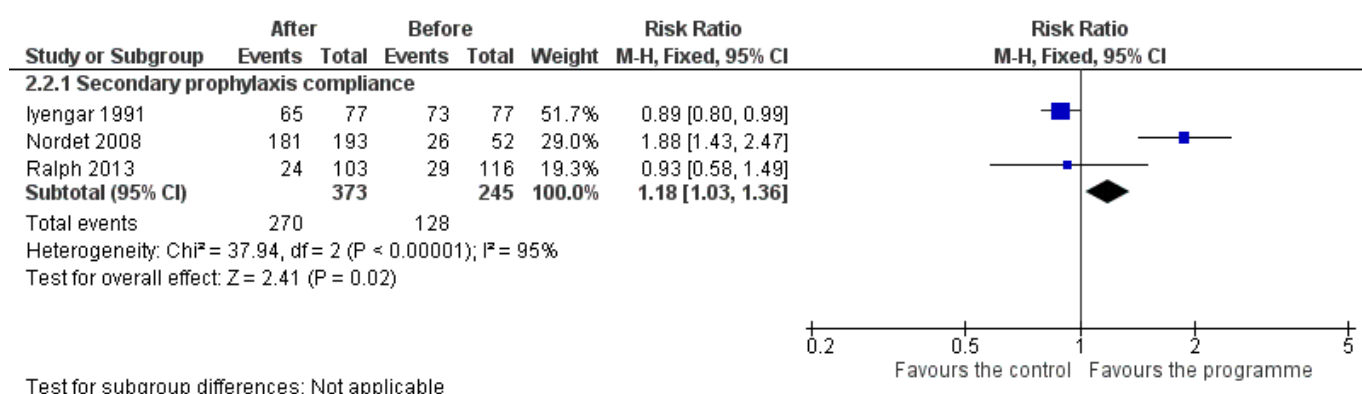


Figure 2B: The effect of an integrated programme on ARF secondary prophylaxis compliance.

3.6 Risk of Bias

The risk of bias assessment is presented in **Table 4**. Overall, two studies were found to have a low risk of bias while the remaining three studies were unclear. In two of the studies, it was unclear whether the outcome measure was accurately measured to minimise bias. One study inadequately described their method of cohort recruitment.

Table 4: Risk of bias assessment using the CASP tool [14]

	Iyengar 1991	Kwan 2013[19]	Nordet 2008[16]	Ralph 2013[18]	WHO 1992[17]
1. Did the trial address a clearly focused issue?	Y	Y	Y	Y	Y
2. Was the cohort recruited in an acceptable way?	Y	Y	Y	Unclear	Y
3. Was the exposure accurately measured to minimise bias?	n/a	n/a	n/a	n/a	n/a
4. Was the outcome accurately measured to minimise bias?	Y	Y	Unclear	Y	Unclear
5. a. Have the authors identified all important confounding factors? b. Have they taken account of the confounding factors in the design and/or analysis?	Y	n/a	n/a	n/a	n/a
6. a. Was the follow up of subjects complete enough? b. was the follow up of subjects long enough?	Y	Y	n/a	n/a	n/a
Overall risk of bias	Low	Low	Unclear	Unclear	Unclear

4. DISCUSSION

4.1 Principal Findings

This systematic review provides the first structured assessment of the extent of integration of RHD programmes into country health systems. We also collected information on programme inputs, activities, outputs, outcomes, and impact, but due to the limitations in the designs of the included studies we were not able to assess the association between programme design, programme integration, and population health outcomes. While most of the RHD programmes specified different outcomes, each demonstrated improved outcomes following programme implementation.

A meta-analysis of secondary prophylaxis adherence showed a statistically significant 18% improvement in adherence ($p=0.02$) following the introduction of integrated RHD programmes in Cuba, India, and Australia. The programmes in Cuba and India both had an education component which targeted healthcare personnel, while in India this was

expanded to teachers and pupils. Both programmes also established a dedicated register to monitor patients with ARF and RHD and to administer prophylaxis. In contrast, the programme in Australia focused on improving clinical practice when diagnosing and managing patients with heart failure, including RHD. Therefore, there appears to be multiple channels for improving prophylaxis compliance which may include education about the disease, a register, or improved implementation of local ARF/RHD guidelines.

None of the programmes were fully integrated, but they did share similarities in the nature and extent of integration into the local health system. The public sector usually took primary responsibility for financing of programmes and for providing clinical care itself, but planning of the RHD programme was never coordinated with the planning of other disease programmes or general health services. Monitoring and evaluation was also not integrated into existing health systems, and demand generation (understood to mean education of at-risk populations) was usually accomplished using a partially integrated approach. The results of this study are in agreement with a similar review which examined the extent and nature of integration for a number of other disease programmes, and found a heterogeneous picture of integration according to the critical health systems functions.[20]

4.2 Strengths and Limitations of the Review

The main strength of this review is that it provides a unique and comprehensive analysis of programme integration into the health systems while also providing the details of each programmes inputs, activities, outputs and outcomes. This makes the review relevant to the global agenda of scaling up RHD prevention and care initiatives.

There are a number of limitations of this review. Firstly, there were date and English language restrictions on the searches which may have limited the number of publications

found. Secondly, the small number of included studies and the heterogeneity among their outcomes meant that sub-group analysis was not possible. Therefore, explanations cannot be made concerning the effect of integrating the programme according to critical health system functions. It should also be noted that three of the included studies draw from the same overall WHO-developed approach; they all included elements of health education and secondary prophylaxis. It is unclear whether there were overlapping patients studied. In particular, the study by Iyengar in India was conducted at the same time as the WHO multi-country programme (in which India was a participating country).

4.3 Strengths and Limitations in Relation to Other Studies

The findings of this review provide a new synthesis of evidence for the debate on RHD programme implementation. Compared to a prior systematic review of control programmes for communicable, maternal, perinatal, and nutritional diseases, our review found very few published studies on RHD prevention and control programmes.[20]

4.4 Explanations and Implications for Clinicians and Policymakers

The 2018 World Health Assembly resolution on ARF and RHD is indicative of the important health problem RHD poses in many countries; however, there is currently limited evidence for designing efficient programmes to scale up evidence-based interventions. Further, governments are being encouraged to use more horizontal, integrated approaches when designing health programmes.[7] Health planners need reliable evidence upon which to design and implement new RHD initiatives in a manner that is sustainable and synergistic with other health system activities.

Based on existing evidence, we can identify the following best practices across the six key health system functions. The most effective RHD programmes employ **stewardship and**

governance models that involve a dedicated unit, for example within a subnational ministry of health office, which is responsible and accountable specifically for RHD. **Financing** of RHD prevention and treatment interventions should be integrated with general health system resources; external donors wishing to invest in RHD should channel funds through Ministries of Health to ensure efficient purchasing and strengthening of local systems. In the published literature RHD programme **planning** has *not* been integrated with planning for other priority health issues; however, it is unlikely that this approach will be desirable in the future, especially for complex and comprehensive RHD programmes that include a variety of activities ranging from primary prevention to surgery. Published models of care indicate that **service delivery** is best accomplished through the general primary healthcare system, although targeted case-finding activities may be appropriate in some settings, and when these have been conducted in the past, they have made use of dedicated outreach healthcare workers. As mentioned, **monitoring and evaluation** of RHD programmes has typically *not* been integrated, and it is not clear how information systems for ARF and RHD should interact with the rest of the health system (since non-integrated registers, for example, may result in superior patient outcomes). Finally, **demand generation** – understood in this context to mean information, education, and communication – has usually been only partially integrated, such as through dedicated media campaigns and specialised educational activities.

The partially integrated nature of published RHD programmes fits well with the observation that endemic infectious diseases with “elimination” potential may be best addressed eventually through more targeted activities that, as disease incidence declines, can be gradually integrated into the general primary healthcare system.[21] In this way, RHD stands out from other NCDs, for which there is consensus that vertical approaches are

inappropriate.[22] Decision-makers and planners may benefit from thinking about RHD programmes through an infectious disease and elimination framework rather than through a chronic disease framework. This may especially be the case in low-income countries where resources will initially be devoted to primary and secondary prevention rather than cardiac surgery.[23]

4.5 Future Research

The findings of this review provide a starting point for the design and implementation of RHD programmes, but they also highlight some major gaps in knowledge, including a lack of clear evidence on the key programme factors that facilitate integration and still deliver good outcomes. For example, it is recommended that monitoring and evaluation of ARF/RHD secondary prevention activities make use of disease registers. There is no evidence that countries have taken disease registers to scale, and existing reports suggest that such registers have not been integrated into general health information and surveillance systems. Further investigation is required into whether these registers would be more effective if they were integrated into health information systems, or rather as parallel information systems. Comparative research, using prospective quasi-experimental and experimental methods, is needed in order to determine how to optimise the effectiveness of RHD-related health technologies while moving towards fully integrated programme models. Future research should report on the impact of the programme, namely the incidence, prevalence, or mortality, as standard reporting practice. It is also imperative that the local socio-cultural context is seriously considered when designing future RHD prevention and control interventions so that a local evidence-base can be built to directly advise the decision makers of that region or country.

5. CONCLUSION

We present a systematic analysis of RHD prevention and control programmes and their integration into a various country health systems. The programmes presented in this review were partially integrated, similar in the extent and nature of integration, and appear to be beneficial for RHD-related outcomes. While this research provides a starting point for future RHD programme implementation according to the six key health system functions, it also highlights major gaps in the evidence for programme factors that facilitate integration.

6. ACKNOWLEDGEMENTS

6.1. Contribution of Authors

David Watkins and Liesl Zühlke conceived the review. Jessica Abrams drafted the protocol, literature review, and manuscript. Methodological advice was provided by Mark Engel, Leila Abdullahi, and Mary Shelton (librarian). David Watkins guided the technical content and assisted Jessica Abrams with the data extraction and analysis. Mark Engel guided the quantitative analysis. All authors contributed to the editing of subsequent versions of the protocol, literature review, and manuscript.

6.2 Competing Interests

None.

6.3 Funding

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PART D: APPENDIX

APPENDIX 1: PRISMA 2009 Checklist (Manuscript)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1 - 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4 - 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5 - 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 - 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6 – 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9 – 11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	22 – 23
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12 – 14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	22 – 23

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	21 – 22
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	23 – 24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	24 – 25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	25 - 28
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	28

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

APPENDIX 2: Comprehensive Search Strategy

Subject		Search Terms
PubMed search strategy		
#1	Group A Streptococcus, rheumatic fever, rheumatic heart disease	Pharyngitis[MeSH Terms] OR rheumatic heart disease[MeSH Terms] OR rheumatic fever[MeSH Terms] OR pharyng*[Title/Abstract] OR "sore throat"[Title/Abstract] OR "group A strep*" [Title/Abstract] OR "rheumatic fever"[Title/Abstract] OR "rheumatic heart disease"[Title/Abstract] OR RHD[Title/Abstract]
#2	Health service delivery	(preventative health services[MeSH Terms]) OR delivery of health care, integrated[MeSH Terms]) OR healthcare[Title/Abstract]) OR health care[Title/Abstract]) AND (vertical[Title/Abstract] OR horizontal[Title/Abstract] OR integrated[Title/Abstract] OR coordinat*[Title/Abstract] OR co-ordinat*[Title/Abstract] OR program*[Title/Abstract] OR service*[Title/Abstract])
Search		1 AND 2
Filters: Publication date from 1 January 1990 to 31 December 2017.		
Scopus		
#1	Group A Streptococcus, rheumatic fever, rheumatic heart disease	(TITLE-ABS-KEY (pharyngitis) OR TITLE-ABS-KEY ("rheumatic fever") OR TITLE-ABS-KEY ("rheumatic heart disease") OR TITLE-ABS-KEY ("sore throat") OR TITLE-ABS-KEY ("group A strep*") OR TITLE-ABS-KEY (rhd))
#2	Health service delivery	((TITLE-ABS-KEY (delivery) OR TITLE-ABS-KEY (integrated) OR TITLE-ABS-KEY (program*) OR TITLE-ABS-KEY (programme*) OR TITLE-ABS-KEY (service*) OR TITLE-ABS-KEY (horizontal) OR TITLE-ABS-KEY (vertical))) AND ((TITLE-ABS-KEY (health AND care) OR TITLE-ABS-KEY (healthcare)))
Search		1 AND 2
Filters: Publication date from 1 January 1990 to 31 December 2017.		
EBSCO Host (Africa Wide, CINAHL, and Health Source: Nursing/Academic Edition)		
#1	Group A Streptococcus, rheumatic fever, rheumatic heart disease	AB "rheumatic heart disease" OR AB "rheumatic fever" OR AB "group A strep*" OR AB pharyng* OR AB "sore throat"
#2	Health service delivery	AB delivery of health care, integrated OR AB health care OR AB healthcare AND AB vertical OR AB horizontal OR AB integrated OR AB coordinat* OR AB co-ordinat* OR AB program* OR AB service*
Search		1 AND 2
Filters: Publication date from 1 January 1990 to 31 December 2017.		
ISI Web of Science		
1	Group A Streptococcus, rheumatic fever, rheumatic heart disease	TOPIC: ("rheumatic heart disease") OR TOPIC: ("rheumatic fever") OR TOPIC: ("group A strep*") OR TOPIC: (pharyng*) OR TOPIC: ("sore throat")
2	Health service delivery	(health care) OR TOPIC: (health care) AND TOPIC: (vertical) OR TOPIC: (horizontal) OR TOPIC: (coordinat*) OR TOPIC: (co-ordinat*) OR TOPIC: (integrated) OR TOPIC: (program*) OR TOPIC: (service*)
Search		1 AND 2
Filters: Publication date from 1 January 1990 to 31 December 2017.		

APPENDIX 3: Data Extraction Form

A. General Information

Study ID (<i>first author surname and year of publication e.g. Atun, 2009</i>)	
Date form completed (dd/mm/yyyy)	
Name of data extractor	
Reference citation	
Study author contact details	
Publication type (e.g. full report, abstract)	
Potentially eligible studies found in the reference list	
Notes:	

B. Eligibility criteria

Study characteristics	Eligibility criteria (circle)	Criteria met?
Type of study	RCT, CCT, CBA, ITS, quasi-experimental, cross-sectional.	Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>
Intervention	A coherent and intentional effort to expand health services to the population at risk for GAS, RF, RHD	Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>
Types of outcome measures <i>Include studies providing sufficient info on objectives #1 and #2. The secondary outcome #3 does not have to be met but should be recorded so that we can report the % of studies that does meet #3.</i>	1. Programme characteristics <i>Programme start year, location(s), duration, area of emphasis (services delivered), inputs</i>	Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>
	2. Programme integration <i>6 key functions of the health system (stewardship & governance, financing, planning, service delivery, M&E, demand generation)</i>	Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>
	3. Programme results <i>Outputs (volume and scope of services produced) and outcomes (such as time in therapeutic INR range, adherence to secondary prophylaxis, or proportion of the population covered)</i>	Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>
<p style="text-align: center;"> INCLUDE <input type="checkbox"/> EXCLUDE <input type="checkbox"/> PENDING <input type="checkbox"/> </p>		
Reason(s) for exclusion/pending:		
Notes:		

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

C. Characteristics of included studies

	Description as stated in the paper/report
Objective(s) of study	
Brief description of intervention(s) or model(s) studied	
Study design	
Country, province/state (if known)	
Notes:	

D. Outcome measures

I. Programme characteristics

	Description as stated in the paper/report
Start year	
Duration (<i>recruitment – last follow-up</i>)	
Number of patients seen in the programme	
Primary prevention component? Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>	If yes, provide details:
Secondary prevention component? Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>	If yes, provide details:
Tertiary prevention component? Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>	If yes, provide details
Inputs (Organised according to WHO “building blocks” framework) When possible, provide quantitative data, e.g., budget of US\$ 100,000 per year; 30 nurses trained during the programme's duration	Leadership/administration: Unclear/not stated <input type="checkbox"/>
	Financing - source(s) and amount(s): Unclear/not stated <input type="checkbox"/>
	Healthcare workers (types and numbers): Unclear/not stated <input type="checkbox"/>
	Technologies (drugs, diagnostics, etc.) Unclear/not stated <input type="checkbox"/>
	Information systems (medical records, etc.)

	Unclear/not stated <input type="checkbox"/>
	Systems of care delivery (guidelines, protocols, etc.) Unclear/not stated <input type="checkbox"/>

II. Extent of programme integration

Critical health system function (Elements)	Extent of integration
Stewardship & Governance (Accountability function; reporting; performance management)	Fully <input type="checkbox"/> Partially <input type="checkbox"/> Not integrated <input type="checkbox"/> Unknown <input type="checkbox"/> Notes:
Financing (Pooling of funds; provider payment methods)	Fully <input type="checkbox"/> Partially <input type="checkbox"/> Not integrated <input type="checkbox"/> Unknown <input type="checkbox"/> Notes:
Planning (needs assessment; priority setting; resource allocation)	Fully <input type="checkbox"/> Partially <input type="checkbox"/> Not integrated <input type="checkbox"/> Unknown <input type="checkbox"/> Notes:
Service delivery (Structural; human resources; shared infrastructure; operational integration; referral and counter-referral systems; guidelines or care pathways; procurement; supply chain management)	Fully <input type="checkbox"/> Partially <input type="checkbox"/> Not integrated <input type="checkbox"/> Unknown <input type="checkbox"/> Notes:
Monitoring and evaluation (Information technology infrastructure; data collection and analysis)	Fully <input type="checkbox"/> Partially <input type="checkbox"/> Not integrated <input type="checkbox"/> Unknown <input type="checkbox"/> Notes:
Demand generation (Financial incentives e.g. conditional cash transfers, insurance; population interventions e.g. education and promotion)	Fully <input type="checkbox"/> Partially <input type="checkbox"/> Not integrated <input type="checkbox"/> Unknown <input type="checkbox"/> Notes:
Other notes:	

III. Programme results

	Description as stated in the paper/report
Outputs (<i>goods and services produced and delivered</i>) – quantify when possible	

Primary prevention component	
Secondary prevention component	
Tertiary prevention component	
Outcomes (<i>use of outputs by targeted population</i>) – quantify when possible	
Primary prevention component	
Secondary prevention component	
Tertiary prevention component	
Impact (<i>change in health of targeted population</i>) – experimental and quasi-experimental designs only	
Primary prevention component	
Secondary prevention component	
Tertiary prevention component	

E. Risk of bias assessment

I. Observational studies

Questions	Judgement (yes/no/unclear)	Description
Are the results of the trial valid?		
7. Did the trial address a clearly focused issue?		
8. Was the cohort recruited in an acceptable way?		
9. Was the exposure accurately measured to minimise bias?		
10. Was the outcome accurately measured to minimise bias?		
11. a. Have the authors identified all important confounding factors? b. Have they taken account of the confounding factors in the design and/or analysis?		
12. a. Was the follow up of subjects complete enough? b. was the follow up of subjects long enough?		
What are the results?		
13. What are the results of the study?		
14. How precise are the results?		
15. Do you believe the results?		
Will the results help locally?		
16. Can the results be applied to the local population?		
17. Do the results fit with other available evidence?		
18. What are the implications of this study for practice?		

II. Experimental studies

Questions	Judgement (yes/no/unclear)	Description
Are the results of the trial valid?		
19. Did the study address a clearly focused issue?		
20. Was the assignment of patients to treatments randomised?		
21. Were all of the patients who entered the trial properly accounted for at its conclusion?		
22. Were patients, health workers and study personnel 'blind' to treatment?		
23. Were the groups similar at the start of the trial?		
24. Aside from the experimental intervention, were the groups treated equally?		
What are the results?		
25. How large was the treatment effect?		
26. How precise was the estimate of the treatment effect?		
Will the results help locally?		
27. Can the results be applied in your context/to the local population?		
28. Were all clinically important outcomes considered?		
29. Are the benefits worth the harms and costs?		

APPENDIX 4: Criteria for Determining the Extent of Integration for each Health System Function

	Fully integrated (score = 3)	Partially integrated (score = 2)	Not integrated (score = 1)
Stewardship and Governance <i>Oversight and guidance.</i>	When the governance arrangements for the intervention are the same as those for the general health services or the local or national administrative structures.	The responsibility is shared by the existing general health care system and a specific structure created purposely for the intervention.	When accountability remains exclusively with dedicated specialist entities charged with implementation and management of health interventions, without involvement of the general health care system.
Financing <i>The pooling of financial resources and the provider-payment methods used to allocate these.</i>	Funding is provided entirely through the national or regional general health care budget.	For example, where earmarked funding was provided by the United States Agency for International Development (USAID) but channelled through the PHC system.	When financing is provided directly to an intervention and addressing only a particular disease or problem; or directly funded by an external donor.
Planning <i>Activities, processes and systems for needs assessment, priority setting, and resource allocation.</i>	If the decision-making in relation to the above three areas is undertaken by institutions/stakeholders who are involved in the same tasks for the general health system.	Decision-making responsibility for planning is retained by those managing the health intervention but involves a range of stakeholders (such as civil society representatives, PHC level, or local/regional/national government) through inclusive groupings.	When the decision-making focused solely on the intervention without consideration of general health care activities. This may include specific national government units at national level.
Service delivery <i>Structural and organizational dimensions of the programme.</i>	If their provision is the responsibility of general or multi-purpose health worker.	Where there is shared responsibility for the provision of services between general health workers and the health intervention staff; purpose trained volunteers; when service delivery for a number of interventions is linked.	A number of interventions rely solely on single purpose workers and have no integration with other interventions or general health services.
Monitoring and Evaluation	Use of shared indicators and establishment of integrated data collection, recording, analysis and reporting systems.	When M&E were undertaken jointly by staff from the regional health services and the control programme.	When M&E is undertaken independently by the sponsor, institution, or volunteers of the implementing organisation.
Demand generation <i>The use of appropriate financial incentives and monetary support, insurance, or information, education and communication activities designed to change behaviour.</i>	If mechanisms used to create financial incentives or education and communication activities are provided jointly with the general services or are delivered by primary health care workers.	When education is provided jointly by the targeted programme staff and regional health workers.	Where information campaigns related to health interventions are stand-alone activities, focusing solely on a single problem or disease, and delivered by single-purpose health workers or volunteers.

From: Atun R, de Jongh T, Secci F, et al. Integration of targeted health interventions into health systems: a conceptual framework for analysis. *Health Policy Plan* 2010;25:104–11. <http://dx.doi.org/10.1093/heapol/czp055>, and Atun R, de Jongh T, Secci F, et al. A systematic review of the evidence on integration of targeted health interventions into health systems. *Health Policy Plan* 2010;25:1–14. <http://dx.doi.org/10.1093/heapol/czp053>.

APPENDIX 5: Ethics Waiver



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E53-48 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338
Email: 1amees,emfedl@uct.ac.za

Website: www.health.uct.ac.za/fl:js/reseacbtbhumanethics/forms

05 January 2017

A/Prof MEngel
Medicine
J Floor
OMB

Dear A/Prof Engel

Project Title: Integrating the prevention and control of rheumatic heart disease into country health system: A systematic review

Thank you for submitting your request to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC notes that the proposed study is a systematic review.

As the systematic review involves published literature available through publicly accessible electronic databases, research ethics review and approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: *"Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research."*

The HREC recommends that researchers refer to the PRISMA website, for the PRISMA statement and checklist, to facilitate the reporting of systematic reviews and meta-analyses. For more information, please refer to <http://www.prisma-statement.org/>.

Further, fundamental ethical principles for health-related research should be considered in the objectives and methods of the systematic review. See, for example, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015).

The HREC acknowledges that the student Ms Jessica Abrams (MPH Student: ABRJES009) will also be involved in this project.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

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A declaration of interests for all authors must be received before an article can be reviewed and accepted for publication. It should take one of two forms, depending on what type of article you are submitting, detailed on the following page.

4. ADDITIONAL REQUIREMENTS BY ARTICLE TYPE

In addition to the above, all of our articles have additional requirements which should be fulfilled before submitting. For more information on any of the requirements below, please contact papersadmin@bmj.com.

4.1 RESEARCH

4.1.1 What kind of research does The BMJ publish?

The BMJ gives priority to articles reporting original, robust research studies that can improve decision making in medical practice, policy, education, or future research and will be important to general medical readers internationally.

Competing interest forms at *The BMJ*

Section	Form information	Example statements
Editorials and Education articles (including State of the Art reviews and Therapeutics)	<p>Since 2014, <i>The BMJ</i> requires that such articles must be written by authors without relevant financial ties to industry. By “industry” we mean companies producing drugs, medical foods, nutraceuticals, devices, apps or tests; medical education companies; or other companies with a financial or reputational interest in the topic of the article. We consider the following relationships with industry to be relevant, making it unlikely that we would be able to publish your work: employment; ownership of stocks and shares (this excludes mutual funds or other situations in which the person is not in a position to control investment decisions); travel and accommodation expenses; paid consultancy or directorship; patent ownership; aid membership of speakers’ panels or bureaus and advisory board; acting as an expert witness; being in receipt of a fellowship, equipment, writing, or administrative support; writing or consulting for a medical education promotional or communications company. If you are in doubt about the relevance of any potential conflict of interest please discuss with the editor of the appropriate section before submission.</p> <p>All authors must review the updated COI policy and complete The BMJ’s Education Declaration of Interests form. If the article is accepted for publication these completed forms will be stored and made available on request. The corresponding author should insert within their manuscript a summary statement derived from the information provided in the COI forms (link below): “/We have read and understood BMJ policy on declaration of interests and declare the following interests: [list them or state that you have none].”</p>	<ul style="list-style-type: none"> No competing interests: “We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.” Competing interests disclosed: “We have read and understood BMJ policy on declaration of interests and declare the following interests: AA is an unpaid member of XX group developing guidelines for ZZ.”
Research and RMR articles	<p>We ask authors of research papers to use a revised version of the ICMJE’s unified disclosure form. The unified form can be used for several journals. Each journal, will, however, integrate the form into its processes in different ways.</p> <p>Authors must disclose three types of information:</p> <ul style="list-style-type: none"> Associations with commercial entities that provided support for the work reported in the submitted manuscript (the timeframe for disclosure in this section of the form is the lifespan of the work being reported). Associations with commercial entities that could be viewed as having an interest in the general area of the submitted manuscript (in the three years before submission of the manuscript). Non—financial associations that may be relevant or seen as relevant to the submitted manuscript. <p>All authors must complete the disclosure form and send it to the corresponding author who will use the information in the forms to craft the COI statement for the paper (examples provided below). The statement but not the forms must be included with the submission, and that must be included with the initial submission. If the paper is accepted, these forms will be required and will be published alongside the article.</p> <p>The statement in the manuscript should take the following format: <i>“Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work [or describe if any]; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years [or describe if any]; no other relationships or activities that could appear to have influenced the submitted work [or describe if any].”</i></p>	<ul style="list-style-type: none"> No competing interests: “All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.” Grant funding for research but no other competing interest: “All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from ABC Company for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.” Mixed competing interests: “All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; AB has received research grants and honorariums from XYZ company, BF has been paid for developing and delivering educational presentations for BBB foundation, DF does consultancy for HHH and VVV companies; no other relationships or activities that could appear to have influenced the submitted work.”
All other articles	<p>Complete <i>The BMJ’s</i> Disclosure form. We do not need to receive signed copies of the statements regarding competing interests or the licence to publication: these are for information only. When submitting your article (or a revised version of it) you will be prompted at our online editorial office to tick two boxes, confirming that you have read and complied with our policies on competing interests and licence to publication. Please also ensure that your manuscript, whether in original or revised form, also includes your written statements of competing interests and licence to publication.</p>	

The BMJ welcomes studies that will aid the translation of knowledge and implementation of evidence into practice and policy, and is particularly interested in evaluations of the comparative effectiveness of interventions. This knowledge may be most relevant to the day to day decisions doctors make with patients, to public health, or to policy decisions about healthcare.

To learn more about the kind of research articles we give priority to, and what services we offer to authors of research, please read the editorial “[Publishing your research study in the BMJ?](#)”. Please note that we welcome studies — even with “negative” results — as long as their research questions are important, new, and relevant to general readers and their designs are appropriate and robust.

Word count and style

To encourage full and transparent reporting of research we do not set fixed word count limits for research articles. Nonetheless, we ask you to make your article concise and make every word count. You will be prompted to provide the word

count for the main text (excluding the abstract, references, tables, boxes, or figures) when you submit your manuscript.

Original research articles should follow the IMRaD style (introduction, methods, results, and discussion) and should include a structured abstract (see below), a structured discussion, and a succinct introduction that focuses — in no more than three paragraphs — on the background to the research question.

For an intervention study, the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice, please also provide any relevant detailed descriptions and materials (uploaded as one or more supplemental files, including video and audio files where appropriate). Alternatively, please provide URLs to openly accessible websites where these materials can be found.

Please ensure that the discussion section of your article comprises no more than a page and a half and follows this overall structure, with subheadings:

- Statement of principal findings
- Strengths and weaknesses of the study
- Strengths and weaknesses in relation to other studies, discussing important differences in results
- Meaning of the study: possible explanations and implications for clinicians and policymakers
- Unanswered questions and future research

Structured abstract

Please ensure that the structured abstract is as complete, accurate, and clear as possible and has been approved by all authors. We may screen original research articles by reading only the abstract.

Abstracts should be 250—300 words long: you may need up to 400 words, however, for a CONSORT or PRISMA style abstract. MEDLINE can now handle up to 600 words. Abstracts should include the following headings, but they may be modified for abstracts of clinical trials or systematic reviews and meta-analyses according to the requirements on the [CONSORT extension for abstracts](#) and the [PRISMA extension for abstracts](#), respectively.

- **Objectives** — a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- **Design** — including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- **Setting** — include the level of care, eg primary, secondary; number of participating centres. Be general rather than give the name of the specific centre, but give the geographical location if this is important
- **Participants** (instead of patients or subjects) — numbers entering and completing the study, sex, and ethnic group if appropriate. Give clear definitions of how selected, entry and exclusion criteria.
- **Interventions** — what, how, when and for how long. This heading can be deleted if there were no interventions but should normally be included for randomised controlled trials, crossover trials, and before and after studies.
- **Main outcome measures** — those planned in the protocol, those finally measured (if different, explain why).
- **Results** — main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- **Conclusions** — primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article. Conclusions are important because this is often the only part that readers look at.
- **Trial registration** — registry and number (for clinical trials and, if available, for observational studies and systematic reviews).

When writing your abstract, use the active voice but

avoid “we did” or “we found”. Numbers over 10 do not need spelling out at the start of sentences. P values should always be accompanied by supporting data, and denominators should be given for percentages. Confidence intervals should be written in the format (15 to 27) within parentheses, using the word “to” rather than a hyphen. Abstracts do not need references.

Statistical issues

We want your piece to be easy to read but also as scientifically accurate as possible. We encourage authors to review the [“Statistical Analyses and Methods in the Published Literature or The SAMPL Guidelines”](#) while preparing their manuscript.

Whenever possible, state absolute rather than relative risks.

Please include in the results section of your structured abstract (and in the article’s results section) the following terms, as appropriate:

For a clinical trial:

- *Absolute event rates among experimental and control groups.*
- *RRR (relative risk reduction).*
- *NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000).*

For a cohort study:

- *Absolute event rates over time (eg 10 years) among exposed and non-exposed groups*
- *RRR (relative risk reduction)*

For a case control study:

- *OR (odds ratio) for strength of association between exposure and outcome*

For a study of a diagnostic test:

- *Sensitivity and specificity*
- *PPV and NPV (positive and negative predictive values)*

The box stating what is known and what this study adds (see below) should also reflect accurately the above information. Under what this study adds, please give the one most useful summary statistic eg NNT.

Please do not use the term ‘negative’ to describe studies that have not found statistically significant differences, perhaps because they were too small. There will always be some uncertainty, and we hope you will be as explicit as possible in reporting what you have found in your study. Using wording such as “our results are compatible with a decrease of this much or an increase of this much” or ‘this study found no effect’ is more accurate and helpful to readers than “there was no effect/no difference.” Please use such wording throughout the article, including the structured abstract and the box stating what the paper adds.

Provide one or more references for the statistical package(s) used to analyse the data — for example, RevMan for a

Submitting a BMJ Research article

All BMJ Research articles should be submitted through our submission system at [submit.bmj.com](#). Completed ICMJE forms are required for ALL Research authors

Research article checklist

We have produced a checklist on [bmj.com](#) to help you decide whether *The BMJ* is the right journal for your work.

Another resource, the [Authors' Submission Toolkit: A practical guide to getting your research published](#), summarises general tips and best practices to increase awareness of journals' editorial requirements, how to choose the right journal, submission processes, publication ethics, peer review, and effective communication with editors.

If your work does not seem to fit in *The BMJ* you may prefer to try another journal with a more specialist or local readership, or a higher acceptance rate.

systematic review. There is no need to provide a formal reference for a very widely used package that will be familiar to general readers — for example, Stata — but please say in the text which version you used.

Reporting checklists and guidelines

Reporting guidelines promote clear reporting of methods and results to allow critical appraisal of the manuscript. We ask that all manuscripts be written in accordance with the appropriate reporting guideline. Please submit as supplemental material the appropriate reporting guideline checklist showing on which page of your manuscript each checklist item appears. A complete list of guidelines can be found in the website of the Equator Network. Below is the list of most often used checklists but others may apply.

RECOMMENDED REPORTING GUIDELINES

Clinical trials: For a clinical trial, use the [CONSORT checklist](#) and also include a structured abstract that follows the CONSORT extension for abstract checklist, the CONSORT flowchart and, where applicable, the appropriate CONSORT extension statements (for example, for cluster RCTs, pragmatic trials, etc.). A completed [TIDieR checklist](#) is also helpful as this helps to ensure that trial interventions are fully described in ways that are reproducible, usable by other clinicians, and clear enough for systematic reviewers and guideline writers.

Systematic reviews and meta-analysis: For systematic reviews or meta-analysis of randomised trials and other evaluation studies, use the [PRISMA checklist](#) and flowchart and use the PRISMA structured abstract checklist when writing the structured abstract.

Diagnostic accuracy: [STARD checklist](#) and flowchart
Observational studies: For observational studies, use the [STROBE checklist](#) and any appropriate extension STROBE extensions.

Genetic risk prediction: [GRIPS guidelines](#).

Economic evaluation studies: [CHEERS guidelines](#).

Prediction models: For studies developing, validating or updating a prediction model, use [TRIPOD](#).

For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the [GRADE system](#).

Cover letter

A cover letter is your opportunity to introduce your study to the editor, highlighting the most important findings and novelty. Please include the following information:

- Details of previous publications from the same study — including in scientific abstracts or partial reports by the media at scientific meetings and in foreign language journals.
- Details of any previous publication of the same study in electronic form, including on any preprint server. *The BMJ* does not [consider posting of protocols and results in clinical trials registries to be prior publication](#), but

we would like to know if results have been posted, and where (please provide URLs or trial registration details). We require protocols for clinical trials that have now been published. We are pleased to consider articles based on longer systematic reviews and meta-analyses published at the Cochrane Library or HTA database.

- In most cases, we will follow suggestions for preferred and non-preferred reviewers. If you have suggestions for preferred reviewers, please provide us with their names and contact details; we may invite some of them to review the paper. Please also let us know if you would not like us to invite specific reviewers to look at your work but provide an explanation for your request.

- Assurance that a study funded or sponsored by industry follows the [guidelines on good publication practice](#). These GPP2 guidelines aim to ensure that such studies are published in a responsible and ethical manner. The guidelines cover companies' responsibility to endeavour to publish results of all studies, companies' relations with investigators, measures to prevent redundant or premature publication, the roles of authors and contributors, and the role of professional medical writers.

- Assurance that any article written by a professional medical writer follows the [guidelines by the European Medical Writers' Association](#) on the role of professional medical writers. The guidelines emphasise the importance of respecting widely recognised authorship criteria, and in particular of ensuring that all people listed as named authors have full control of the content of articles. The role of professional medical writers must be transparent. Please name any professional medical writer among the list of contributors to any article for *The BMJ* (not only original research articles), and specify in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles. Medical writers have professional responsibilities to ensure that the articles they write are scientifically valid and are written in accordance with generally accepted ethical standards.

Additional information that must be included with reports of Clinical Trials

Trial Registration

In accordance with the International Committee of Medical Journal Editors' [Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals](#), *The BMJ* will not consider reports of clinical trials unless they were registered prospectively before recruitment of any participants. For trials that started before 1 July 2005 retrospective registration will be acceptable, but only if completed before submission of the manuscript to the journal. The trial registration number and name of register should be included at the end of the structured abstract. *The BMJ* accepts registration in any registry that is a primary register of the [WHO International Clinical Trials Registry Platform \(ICTRP\)](#) or in ClinicalTrials.gov, which is a data provider to the WHO ICTRP.

Download recommended reporting guidelines directly

All reporting guidelines recommended here are available for full download from our [Instructions for Authors](#) page.

Find out more about reporting trial registration

All recommended trial registration reporting guidance is available to view on our [Instructions for Authors](#) page.

STATEMENTS THAT MUST BE INCLUDED IN RESEARCH SUBMISSIONS

Public and Patient Involvement statement:

The BMJ is encouraging active patient and public involvement in clinical research as part of its [patient partnership strategy](#). This is research which is “co produced” with patients, carers, or members of the public. To support coproduction of research we request that authors provide a Patient and Public Involvement statement in the methods section of their papers. We request this to both encourage the movement and ensure that *BMJ* readers can easily see whether, and if so how, patients and the public were involved in the research. If they were not involved in any way this information should be formally documented in the Patient and Public Involvement statement. As co production of research with patients and the public is relatively new we appreciate that not all authors will have involved them in their studies. We also appreciate that patient/public involvement may not be feasible or appropriate for all papers. We therefore continue to consider papers where they were not involved.

The Patient and Public Involvement statement should provide a brief response to the following questions, tailored as appropriate for the study design reported:

- *At what stage in the research process were patients/public first involved in the research and how?*
- *How were the research question(s) and outcome measures developed and informed by their priorities, experience, and preferences?*
- *How were patients/public involved in the design of this study?*
- *How were they involved in the recruitment to and conduct of the study?*
- *Were they asked to assess the burden of the intervention and time required to participate in the research?*

In addition to considering the points above we advise authors to look at guidance for best reporting of patient and public involvement as set out in the [GRIPP2 reporting checklist](#). Even if patients were not involved in the study described, we suggest that you consider enlisting their help in disseminating the research findings.

If information detailing whether there was patient and public involvement, or not, is missing in the submitted manuscript we will request authors to provide it. Where they have been involved we consider it good practice for authors to name and thank them in the contributorship statement after seeking their permission to do so; and to clearly identify them as patient/public contributors. When they have contributed substantially and meet authorship criteria they should be invited to coauthor the manuscript. Please note also note that it's [The BMJ policy to send relevant research papers for review by patient reviewers alongside academic peer reviewers](#).

Ethics approval:

[All research studies published in *The BMJ* should be morally acceptable](#), and must follow the World Medical Association's [Declaration of Helsinki](#). To ensure this, we aim to [appraise the ethical aspects](#) of any submitted work that involves human participants, whatever descriptive label is given to that work including research, audit, and sometimes debate. This policy also applies on the very rare occasions that we publish work done with animal participants. The manuscript must include a statement that the study obtained [ethics approval](#) (or a statement that it was not required), including the name of the ethics committee(s) or institutional review board(s), the number/ID of the approval(s), and a statement that participants gave informed consent before taking part.

Transparency statement:

Please include in your manuscript a [transparency declaration](#): a statement that the lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained. *The BMJ* is committed to making the editorial process transparent and ethical. *The BMJ*'s transparency policies are [accessible from this link](#).

Role of the funding source:

Please include in the funding statement a statement giving the details of all sources of funding for the study. As appropriate, the statement must include a description of the role of the study sponsor(s) or funder(s), if any, in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. In addition, the statement must confirm the independence of researchers from funders and that all authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis is also required.

If you are submitting an original article reporting an industry sponsored clinical trial, postmarketing study, or other observational study please follow the [guidelines on good publication practice \(GPP2\)](#) and on properly reporting the role of [professional medical writers](#). Another resource, the [“Authors’ Submission Toolkit: A practical guide to getting your research published”](#) summarises general tips and best practices to increase awareness of journals’ editorial requirements, how to choose the right journal, submission processes, publication ethics, peer review, and effective communication with editors — much of which has traditionally been seen as mysterious to authors.

The BMJ will not consider for publication any study that is partly or wholly funded by the tobacco industry, as explained in [this editorial](#).

SUMMARY BOXES

Please produce a box offering a thumbnail sketch of what your article adds to the literature. The box should be divided into two short sections, each with 1—3 short sentences.

Section 1: What is already known on this topic

In two or three single sentence bullet points, please summarise the state of scientific knowledge on this topic before you did your study, and why this study needed to be done. Be clear and specific, not vague.

Section 2: What this study adds

In one or two single sentence bullet points, give a simple answer to the question “What do we now know as a result of this study that we did not know before?” Be brief, succinct, specific, and accurate. For example: “Our study suggests that tea drinking has no overall benefit in depression.” You might use the last sentence to summarise any implications for practice, research, policy, or public health. DO NOT make statements that are not directly supported by your data.

Datasharingwith Dryad

The BMJ has partnered with the Dryad digital repository datadryad.org to make open deposition easy and to allow direct linkage by doi from the dataset to *The BMJ*'s article and back (for *The BMJ*'s articles' datasets see here)

Data sharing

We require a data sharing statement for all research papers. For papers that do not report a trial, we do not require that authors agree to share the data, just that they will say whether they will.

For reports of clinical trials, we ask that the authors commit to making the relevant anonymised patient level data available on reasonable request ([see editorial](#)). This policy applies to any research article that reports the main endpoints of a randomised controlled trial of one or more drugs or medical devices in current use, whether or not the trial was funded by industry.

"Relevant data" encompasses all anonymised data on individual patients on which the analysis, results, and conclusions reported in the paper are based. As for "reasonable request," *The BMJ* is not in a position to adjudicate, but we will expect requesters to submit a protocol for their re-analysis to the authors and to commit to making their results public. We will encourage those

requesting data to send a rapid response to thebmj.com, describing what they are looking for. If the request is refused we will ask the authors of the paper to explain why.

In addition, we will follow the [new ICMJE data sharing policy](#) that goes into place on July 1, 2018 (see editorial): manuscripts submitted to ICMJE journals that report the results of clinical trials must contain a data sharing statement that indicates whether individual de-identified participant data (including data dictionaries) will be shared; what data in particular will be shared; whether additional, related documents will be available (study protocol, statistical analysis plan, etc); when the data will become available and for how long; by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Clinical trials that begin enrolling participants on or after January 1, 2019 must also include a data sharing plan in the trial's registration. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record.

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OPEN ACCESS FOR RESEARCH

All research papers in *The BMJ* are published with Open Access. Open access articles may be reused according to the relevant Creative Commons licence. *The BMJ*'s default licence for open access publication of research is the [Creative Commons Attribution Non Commercial licence \(CC BY—NC 4.0\)](#). But where the funder requires it the author can select the [Creative Commons Attribution \(CC BY 4.0\)](#) licence during the submission process (funders who mandate CC BY include the Wellcome Trust, RCUK, and MRC).

To support this, we ask authors to pay an open access article publishing charge/fee of £3000/\$4800 (excluding VAT) on acceptance of their paper. We can offer discounts and waivers for authors who cannot pay. Consideration of the paper is not related to whether authors can or cannot pay the fee. We will ask for the fee only once we have accepted a paper, and we will send an invoice only once authors tell us. Please do not contact editors about open access fees: neither editors nor reviewers will know whether a fee is payable, and administrative staff will handle payments and all associated correspondence.

A number of institutions have open access institutional memberships with BMJ (the publishing group), which either cover the whole cost of open access publishing for authors at participating institutions or allow authors to receive a discount on the article processing charge.

We encourage authors of all research articles in *The BMJ* to link their articles to the raw data from their studies. For clinical trials, we require data sharing on request as a minimum and- if authors of such trials are willing to go further and share the data openly, so much the better.

SUPPLEMENTAL MATERIAL, VIDEO

- Original raw data: If you think they will help our reviewers (and maybe readers), or if we specifically request them. Please note our policy on data sharing, explained above.
- Video, image, table, and audio files: If these add educational value to your article. We may be able to publish additional files on bmj.com.
- Video abstract: These can summarise your findings and will be posted on bmj.com alongside your paper. You can find additional information about video abstracts [in this editorial](#), and [here](#).
- Public and patient involvement materials used in your research
- Copies of any non—standard questionnaires and assessment schedules used in your research
- Copies of patient information sheets used to obtain informed consent for the study, or to comprise or deliver the intervention in a clinical trial
- Copies of closely related articles you've published (particularly important when details of the study are published elsewhere)
- Copies of any previous reviewers' reports on this article

4.2 RESEARCH METHODS AND REPORTING

The BMJ is also interested in original studies on research methodology, research reporting, peer review, and evidence based medicine. The same criteria apply to these as to all the other types of research we consider. We will give priority to studies that will be relevant and interesting to enough of our readers (not only to editors, statisticians, and other experts on methodology) and will help them make better decisions when conducting research; searching for evidence; or using research evidence in their practice, their teaching, or their learning. We also publish essays about designing, conducting, and reporting research, in our [research methods and reporting section](#).

We are willing to consider papers that present new or updated research reporting guidelines, but only if the guideline pertains to a study type that we publish in *The BMJ*. The checklist itself must be included as part of the paper. We prefer to be the only journal publishing the guideline, but under some circumstances we will consider copublication with up to two other journals.

For an example of how to format a reporting guideline to appear in our research methods and reporting section, [see here](#).

Research Methods and Reporting articles should have the elements below.

Word count and style

We do not set fixed word count limits for RMR articles. Nonetheless, we ask you to make your article concise and make every word count. For some submissions this might be published in full on [bmj.com](#) with a shorter version or abstract in the print *BMJ*.

Title and abstract

A short title is followed by an 100—150 word italicised summary (the standfirst) which encapsulates the article's central message.

Introduction

Articles should begin with a brief paragraph that captures readers' attention and explains the aim of the piece.

Text

The body of the text should be broken up under subheadings that provide a logical narrative structure. Avoid acronyms and abbreviations unless they are universally recognised e.g. DNA. The evidence on which key statements are based should be explicit and referenced, and the strength of the evidence (published trials, systematic reviews, observational studies, expert opinion etc.) addressed.

Boxes, tables and figures

Include tables, boxes, or illustrations (clinical photographs, imaging, line drawings, and figures) to enhance the text and add to or substantiate key points made in the body of the article. Figures may be in color. Worked out examples that

use specific methods under discussion can be included as additional boxes. If appropriate, include a box of linked information such as website urls for those who want to pursue the subject in more depth.

Web extras

We may be able to publish on [bmj.com](#) some additional boxes, figures, and references. Please included these as a web reference list in the main article file. You may also include suggestions for linked podcasts or video clips, as appropriate.

Contributors and sources

We ask for a 100—150 word supplementary paragraph (excluded from word count) to explain the article's provenance. It should include the relevant experience and expertise of each author, his or her contribution to the paper, and the sources of information used to prepare it. One author must be nominated as the guarantor of the article. Include a statement of sources and selection criteria.

Key messages box

Include up to four sentences, in the form of short bullet points, highlighting the article's main points.

References

Must be in Vancouver style and should be kept to a minimum; ideally no more than 20.

RESEARCH METHODS AND REPORTING — OPEN ACCESS

Research Methods and Reporting articles are not published as Open Access by default.

If you would like your article to be published with an Open Access licence, we recommend requesting this directly on submission. Standard *BMJ* Open Access fees apply to all Research Methods and Reporting articles published with an Open Access licence. Find out more about our Open Access policy [here](#).

Presubmission enquiries for a BMJ Analysis article

If you are unsure if your work is suitable for *The BMJ*'s Analysis section we are willing to consider succinct pre-submission inquiries, [please complete this form and await a response](#) from one of the analysis editors.

4.3 ANALYSIS

The Analysis section of the journal is a forum for scholarly debate articles which discuss topical clinical, scientific, ethical, and policy issues that matter to doctors and patients. We look for our analysis articles to be interesting and thought-provoking to a broad range of readers based all over the world, including policy makers, doctors of all specialties, and other healthcare professionals. They should present a clearly reasoned argument, backed by an even-handed look at the evidence, with a clear key message. Articles that set out hypotheses are not suitable unless they contain a convincing attempt to test them.

Analysis articles should have the following elements:

Word count and style

The BMJ has an international readership that includes policy makers, health professionals, and doctors of all disciplines. Authors are advised to keep this readership in mind and to write their article for the non-expert. It's important to avoid jargon. Specialised terminology and references to organisations or practices that are specific to one country need to be explained. Clear writing and an attractive presentation are essential. Analysis papers should be 1800–2000 words long.

Title, standfirst and introduction

A short title is followed by an italicised single sentence (the standfirst) which encapsulates the article's central message. Articles should begin with a brief paragraph that captures readers' attention and explains the aim of the piece.

Text

The body of the text should be broken up under sub-headings that provide a logical narrative structure. Avoid acronyms and abbreviations unless they are universally recognised eg. DNA. The evidence on which key statements are based should be explicit and referenced, and the strength of the evidence (published trials, systematic reviews, observational studies, expert opinion, etc.) made clear. Articles should present a balanced, even-handed look at the evidence rather than selectively citing evidence that supports a particular view.

Boxes, tables and figures

These should extend and substantiate points made in the body of the paper. Any additional material should be concise.

Key messages box

This should be at the end of the article and include 2 to 4 points summing up the main conclusions. When submitting your article at [submit.bmj.com](#), please enter your key messages when prompted to enter the abstract.

References

Must be in Vancouver style and should be kept to a minimum; ideally no more than 20.

Contributors and sources

We ask for a 100–150 word supplementary paragraph (excluded from word count) to explain the article's provenance. It should include the relevant experience and expertise of each author, his or her contribution to the paper, and the sources of information used to prepare it. One author must be nominated as the guarantor of the article. You are welcome to invite co-authors to work with you on the article. We suggest including 2–3 co-authors with different locations and perspectives to help ensure articles are international in scope and accessible to our broad readership online and in print.

Report of patient involvement

As *The BMJ* is seeking to advance [partnership with patients](#), we also ask authors to seek their input into articles wherever relevant, and document their involvement as patient contributors or coauthors.

Conflicts of Interest

All authors should read our competing interests policy and include the appropriate declaration in their manuscript. Where a competing interest exists that might disqualify an author from contributing, it is wise to discuss it with a BMJ editor before writing the article.

Licence

We require the manuscript to include the following statement:

"The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd ("BMJ"), and its Licensees to permit this article (if accepted) to be published in The BMJ's editions and any other BMJ products and to exploit all subsidiary rights, as set out in [our licence](#)."

Peer review

The BMJ has fully open peer review for analysis articles. This means that every accepted analysis article submitted will have its prepublication history posted alongside it on [thebmj.com](#). This prepublication history comprises all previous versions of the manuscript, the report from the manuscript committee meeting, the reviewers' signed comments, and the authors' responses to all the comments from reviewers and editors. Authors are welcome to suggest names of suitable reviewers, including patient reviewers.

Post-submission

- All submissions are read in full by one or more members of the editorial team.
- Articles that pass the initial editorial screen are sent for external peer review.
- Articles are then discussed at a regular analysis committee meeting where editors make one of three decisions: reject; reject with offer to resubmit; or provisionally accept.

Accepted analysis articles are published online at [bmj.com](#), the canonical version of *The BMJ*. A proportion of accepted analysis articles will also be published in the print journal.

Analysis prepublication history

In most cases we will publish the prepublication history alongside an accepted analysis article. This prepublication history comprises all previous versions of the manuscript, the report from the manuscript committee meeting, the reviewers' comments, and the authors' responses to all the comments from reviewers and editors. In rare instances we may determine after careful consideration that we should not make certain portions of the prepublication record publicly available.

4.4 EDUCATION

The BMJ publishes [different types of educational articles](#) to engage and challenge a range of postgraduate doctors and clinical researchers internationally. We strive to publish articles that are original in their content and/or presentation, and cannot be found elsewhere or in textbooks. We prioritise topics and situations that are common or have serious consequences, have international appeal, and that interest a variety of doctors, including GPs and specialists.

We encourage authors to write in teams, including those from other specialties, professions, and countries. We ask that one author is rooted in the clinical environment of the intended reader. We encourage authors to write in plain English, to be clear about where there is uncertainty, and to include numbers and phrases where possible that will help doctors in conversation with their patients.

Our educational articles are shaped by two initiatives:

- *We believe that financial interests can distort education articles and we minimise or exclude authors who we judge have such a conflict.*
- *We encourage authors to seek input from patients either to inform the scope, develop the content, contribute to, or co—author articles.*

Submission process and presubmission enquiries

We receive more articles and suggestions than we can publish. We require all authors to submit proposals using the forms to the left, which pose the following questions:

- *What is your idea?*
- *Can you sum up the aim of your article in a sentence?*
- *Why is the topic important to The BMJ's readers?*
- *What is the prevalence of the symptom/condition/situation you wish to write about?*
- *Why cover it now? Has something new happened?*
- *What has The BMJ's Education section covered on this topic in the last five years? What will your contribution add?*
- *Can you provide the key evidence/references you might use?*
- *Why are your writing team well placed to cover the topic?*
- *Have you thought about what a patient would say about your idea?*

POLICIES FOR EDUCATION ARTICLES

Authorship

Education articles can have up to four authors. One author should be from the relevant specialty or setting, unless agreed otherwise. For example, if the article discusses presentation to the emergency department one author should be an emergency care doctor. [All authors should meet authorship criteria](#). We welcome authors or contributions from allied health professions and patient authors, and actively encourage authors from a primary care background.

Competing interests

The BMJ will not consider authors with financial interests when writing Education articles. It is important that we understand the financial interests of every author, and can judge to what extent we believe that they may be relevant to the article that you propose. We do not publish content from authors who [we judge have relevant financial ties to the industry](#) (excluding State of the Art reviews, Therapeutics articles, and Summaries of NICE Guidelines). The relevance of declared interests are judged by the BMJ team. This applies to every author. Any additional authors and their financial interests [must be discussed and agreed with the commissioning editor](#) before the article is submitted.

Patient involvement

As part of our drive to co—produce our content with patients we ask that you [seek patient input](#) into articles at the planning stage.

We ask all authors to what extent patients have been involved in and how involvement has changed an article. We ask that all writing encourages honesty and partnership with patients. Where uncertainty exists, share it. Where data exists present the numbers in a way that can be shared with the patient (absolute numbers, natural frequencies, and graphics). Use language that empowers patients to make the right choices for them in their situation (write that a doctor should/could offer a test, rather than should do a test).

When patients are involved in the manuscript, we ask for their consent. We have two types of consent forms for BMJ education articles:

- [A patient consent form](#) is required if any anonymised patient information is included in the review. Consent is needed for images even if the patients are not identifiable for example, in X—rays and histology slides, and for patients' stories/vignettes even if details are anonymised.
- [A patient contributor form](#) is required for any patients who are named within the review, for example, patient co—authors, patient contributors or named authors of patient stories.

Preparing your manuscript

We want our readers to have the ability to share decisions with their patients and make clear for them the degree of certainty (or lack of it) about a potential course of action. We therefore ask that you follow these recommendations:

- Consider including in your manuscript a box explaining your strategy to search for evidence. It should include a search date, the sources searched, and brief inclusion criteria.
- Clearly distinguish suggestions made based on your experience, standard practice, guidelines, and evidence.
- Provide specifics about the evidence you discuss. For example, for key statements, please say: "A large, well conducted, randomised controlled trial showed INSERT number [CI] and or p value". "The findings of a small case series suggest...". "A subgroup analysis found...". etc.
- Use absolute numbers or explain why you have not used them.
- Consider how these numbers can be communicated by

What do we mean by patient involvement and co—production in Education?

We believe that patient involvement strengthens content. [Read our full guidance on what we mean by patient involvement and co—production.](#)

[Patient consent forms](#)

[Patient contributor forms](#)

Presubmission enquiries for BMJ Education articles

[Education article proposal forms](#)

[Endgames proposal forms](#)

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[BMJ declaration of competing interest forms \(required for ALL Education authors\)](#)

BMJ policies

Find out more about [The BMJ's editorial and ethical policies](#)

*the clinician read to
their patient in a clear
way.*

Education article types

Article Type	Focus/Audience	Content	Word Limit
Clinical Updates	These articles provide an up to date overview of a clinical condition. The content should be evidence based, aimed at non—specialists and have international appeal. It should include a broad update of recent developments (from the past 1—2 years) and their likely clinical applications in primary/community and secondary/hospital care.	There is no strict format to this article type. Consider the use of questions to draw the reader through such as: what are the risk factors? How do patients present? How is it diagnosed? When should we refer patients? How is it managed?	1800 words, maximum of 40 references
Practice Pointer	These are practical, often problem based articles. They should help clinicians who are not specialists in a particular field know "how to" to approach a problem, diagnosis or management better.	There is no strict format to this article type. Consider the use of questions to draw the reader through such as: what are the risk factors? How do patients present? How is it diagnosed? When should we refer patients? How is it managed?	1,000 words and 15 references
Easily Missed	This series highlights conditions that are often missed at first presentation in general practice or the emergency department. For the condition in question provide evidence that the condition may be misdiagnosed or that diagnosis may be delayed and that timely recognition will benefit the patient. The condition should be reasonably common (likely to present at least once a year to a full—time primary care practitioner) or is serious and delayed diagnosis is likely to worsen prognosis. The condition should have easily defined diagnostic features and/or tests with known predictive characteristics.	Include the following subheadings: Case history: Brief fictitious case illustrating how a patient might present and be diagnosed. Introduction: Description of the condition. Outline recent data on incidence, preferably from primary and/or emergency care. Why is it missed? Provide recent evidence of delayed diagnosis or misdiagnosis, which may include audit or medico-legal data if no other evidence is available. Describe factors which contribute to missing this diagnosis. Why does this matter? Describe the consequences of missed diagnosis. How is it diagnosed? Subdivide this into "Clinical features" and "Investigations" that are readily available. Comment on presence, absence and quality of predictive values or sensitivities/specificities (or frequencies for key clinical findings) of the clinical features and investigations mentioned. How is it managed? This should be discussed in 3—4 sentences, as it is not the focus of the series.	1,000 words and 15 references
Rational Testing	These articles update clinicians on the best initial use of imaging methods or diagnostic tests for common or important problems. The aim of these articles is to equip frontline clinicians to exclude and diagnose important conditions, and to know when to refer to a specialist. Imaging articles will require relevant high—resolution images .	Include the following subheadings: The patient: Describe the presentation of a common or important condition whose management will be influenced by ordering the right test. What is the next investigation? List the most important initial tests. Discuss the rationale, limitations and benefits of each, based on the evidence. Include sensitivities/specificities or positive/negative predictive values. Please avoid long lists of differential diagnoses and tests, as these are generally not helpful.	1,000 words and 15 references
10 Minute Consultation	These articles describe how clinicians might use a (one) consultation to tackle a common scenario, in primary or secondary care. Articles must address a tightly framed issue for example how to explore a new symptom (eg tingling fingers), explain a diagnosis of a condition (eg Parkinson's disease, or an aspect of its management) or act in an urgent situation, such as on receipt of a high INR reading.	Include the following subheadings: What to cover. What to do.	700 words and 10 references
Uncertainties	This series highlights areas of practice that lack convincing evidence.	Include the following subheadings: Introduction: Succinctly describe the uncertainty phrased as a question. What is the evidence of uncertainty? Discuss the type and quality of the evidence confirming uncertainty or showing variation in clinical practice. If a relevant systematic review does not exist on this topic, please mention this. Is ongoing research likely to provide relevant evidence? Identify the key research questions that would address the evidence gap (and formulate them in PICO format — population, intervention, comparison, and outcome). Indicate if studies are underway that may address the gap. What should we do in the light of the uncertainty? Provide practical guidance to clinicians on what to do. Include a box of your search strategy for the body text and a second box of the registries you searched to identify forthcoming studies to address the uncertainty	1,000 words and 15 references
Essentials	These articles provide a basic comprehensive summary of a topic that the reader should already know something about. They are aimed at non specialists. Essentials articles are not meant to give readers a full update, and may not be telling readers anything new. Ideally, we prefer an international author team and focus.	The articles follow a broad structure that outlines the evidence and best practice followed by some practical guidance on 'How to do it' perhaps with the use of short fictitious tasters. Authors should present the challenges and include links to other resources.	1,000 words and 15 references.
Therapeutics	The BMJ's Therapeutics series covers new drugs in clinical use or old drugs with important new indications or controversy. Articles are about 1000 words long, and aimed at doctors who aren't specialists in the therapeutic field. They focus on what frontline clinicians need to know before prescribing the drugs, or treating patients already taking them. The editorial that launched the series is here: http://www.bmj.com/content/342/bmj.d37	Detailed structures for this article type will be discussed during the commissioning process between author/editor.	1,000 words and 15 references
Change Page	This series highlights where practice may need to change.	Include the following subheadings: The clinical problem: outline the current diagnostic/treatment approach and its limitations, giving evidence of current practice. End with your actual proposal for change. The evidence for change: include a box of methods (i.e. how you selected the evidence underpinning your proposal.) Indicate the type and quality of the evidence when citing each study. Consider adding a Box describing the pivotal studies. Barriers to change: Describe them (e.g. pragmatic difficulties, risks, contraindications.) How should we change our practice: give a practical description of what changes should be made, based on the evidence.	1,000 words and 15 references

BMJ GUIDANCE FOR AUTHORS: EDUCATION

Article Type	Focus/Audience	Content	Word Limit
What Your Patient Is Thinking (WYPIT)	<p>This is a series led, and edited and written by patients and their carers and contain messages that are thought provoking, and challenging for readers of <i>The BMJ</i>, along the lines of "What I wish you [<i>The BMJ</i>'s audience] knew, and why."</p> <p>Who can write one? Anyone who is using the healthcare system, either on their own behalf or for someone else. To avoid getting overwhelmed by 'doctor as patient' stories, we prioritise pieces from those who are not health professionals. Authors should bear in mind that our readership is international and avoid detailed comments about specific national policies. Some people find it difficult to turn a personal story into something doctors can learn from but if the story is still powerful we are happy to consider publication of articles in another form, for example as a BMJ blogs/opinion piece. If you have an idea for a WYPIT article and want to discuss it before submission please get in touch with BMJ patient editor Sally Carter (scarter@bmj.com) and include an outline of what you would like to say.</p> <p>What these articles are not Complaints about or praise of a named healthcare professional or clinic/hospital; Legal cases which are not resolved; A personal anecdote or journey through the healthcare system with no learning points; Written on behalf of someone else (for example, a carer must write about being a carer, not what they suspect it is like to be the patient) Promotion of a particular treatment or style that other healthcare professionals cannot</p>	<p>Summary Box: "What you need to know" This should include three short bullet points encapsulating the practical things that health professionals might consider doing as a result of reading the article. The editor will work with you to edit the text and may ask doctors working in <i>The BMJ</i> what elements they think are the most powerful to help the article.</p> <p>Other boxes: We are happy to consider a second box containing, for example, useful websites or other learning resources for health professionals. We may also suggest you add some extra explanatory information in a short box if we think the context of your care needs a bit more elaboration.</p> <p>What may be added: Illustrations: Articles are usually published with an accompanying illustration. This is commissioned after the article has been accepted.</p> <p>Questions for Doctors: To encourage ongoing professional learning and development we host a series of reflective questions for doctors based on the content of many of our education article, including WYPITs. These are written by one of the editors and ask the reader what they might do differently having read your article. (The authors of the education articles are not routinely asked to be involved in this process).</p> <p>Content style In the education section of the journal where WYPITs are published we aim to provide up to date and original content to engage and challenge postgraduate doctors and clinical researchers internationally. We ask authors to write in plain English, rather than academic sounding language, and we avoid an over-prescriptive tone. For example, we encourage authors to use words such as 'suggest', 'might', or 'offer' when describing how readers might change their practice (rather than use rigid statements such as 'always', 'never', 'must', 'should').</p> <p>Other considerations We encourage all authors to sign their articles but are happy to discuss anonymity if this is preferred. We also need authors to sign a competing interest form. If you need help in any way with this please let us know.</p>	<p>Around 650 words, including the summary box at the end of each piece, called "What You Need To Know."</p>
Summary of NICE Guidelines	These article types are solely commissioned by our editors.		
State of the Art Reviews			
Minerva Pictures	<p>These are pictures which offer an educational message and which will publish clearly and depict the abnormality obviously. Pictures we are more likely to accept are those which offer an educational message and which will publish clearly and depict the abnormality obviously. Minerva pictures with the following characteristics are not usually accepted because they lack educational value for general readers:</p> <ul style="list-style-type: none"> • Showing foreign bodies • Showing the results of gross trauma • With poor image quality, even if the story is sound and interesting • With pictures and stories which are simply "textbook" presentations • Reporting cases of very rare clinical presentations • Submissions which simply criticise other clinicians, or the patient. <p>Please provide two or three sentences (no more than 100 words) explaining the picture, and please send us the signed consent to publication from the patient. Please make sure that the text includes all authors' names together with their job titles and addresses (including departments' and hospitals' names) at the time the patient was seen, and the email address of the corresponding author. We also need to receive statements of competing interests and copyright/licence.</p> <p>NB: Minerva pictures/articles are not indexed in PubMed.</p>		<p>Less than 100 words</p>
Endgames	<p><i>The BMJ</i> does not publish standard case reports. We do, however, publish articles about real cases if they are suitable for presentation in specific educational formats. These include Endgames case reviews and picture quizzes.</p> <p>Endgames is designed to help doctors across all levels and specialties test their knowledge and reflect on their practice for continuing medical education. Endgames articles are based on genuine clinical scenarios. We only consider common topics rather than clinical rarities (or very rare complications of common diseases, which may be more suitable for BMJ Case Reports journal.) We consider hospital and community based scenarios providing the content is generalisable. We do not publish articles if the patient management is controversial.</p> <p>At least one author must be a specialist (consultant, post CCT, or equivalent) in a field relevant to the topic and all authors must satisfy our strict and competing interest criteria. The online competing interests form must be completed by all authors prior to submission. To avoid duplication of large paragraphs of text from textbooks or journals, we ask authors to provide a signed originality of work attestation form.</p> <p>Which cases are suitable? Please check our archive as we do not repeat topics within 3 years. We only consider common topics rather than clinical rarities and are unlikely to accept an article if the prevalence of the condition is less than 1/100 000 in the population. This includes very rare complications of common diseases, which may be more suitable for BMJ's Case Reports journal. We consider hospital and community based scenarios providing the content is generalisable. We do not publish articles if the patient management is controversial. If you wish to inquire about the suitability of a particular case for Endgames please complete this form.</p>		

BMJ GUIDANCE FOR AUTHORS OF THE OTHER ARTICLE TYPES

Pitching Minerva and Endgames

All Minerva articles should be submitted directly through our online editorial office at submit.bmj.com. Written consent is required from every patient, regardless of whether the patient can be identified or not in the picture.

All Endgame articles should be proposed via our online form, available at [this link](#). Written consent is required from every patient.

ALL EDUCATION ARTICLES REQUIRE

"What you need to know" box

No more than three bullet points for practice articles and five for clinical updates encapsulating the specific take home messages from this article.

"How patients were involved in the creation of this article" box

Please include: Which patients were asked (e.g. patient advocates, networked patient communities and organisations, patients in your clinic etc). What they said (e.g. include more practical advice on how to inject insulin.) How you changed your article as a result (e.g. we included a box to address this.)

"Education into practice" box.

Include two to three bullet points about how a reader might at an individual or organisational level improve their practice (e.g. do you offer lifestyle advice to all patients with newly diagnosed hypertension?)

At least one other box or table and at least one figure or image that complement the text of the article.

4.5 EDITORIALS

These are usually commissioned but we are happy to consider and peer review unsolicited editorials. Please make clear the evidence base of each key statement:

- Expert opinion;
- Personal clinical experience;
- Observational studies;
- Trials; or
- Systematic reviews.

Please include a title page giving all authors' names and corresponding details, as well as statements of competing interests and copyright/licence to publish.

Word count

Up to 800 words long. No more than 12 references

4.6 PERSONAL VIEWS/BMJ OPINION

These original, opinion based essays have a single author. The best personal view pieces make a strong, novel, and well argued point. They are also often topical, insightful, and attention grabbing. We publish anonymous personal view articles only by special arrangement when it would be impossible for the article to appear with the author's name. Accepted articles are all published online initially on [BMJ Opinion](#), but may not be published in print. Please submit online at [http://submit.bmj.com](https://submit.bmj.com). We cannot promise publication before the piece is submitted.

We welcome all submissions for consideration for our [BMJ Opinion blog site](#). Writing should be clear, compelling, and appeal to our international readership. The best pieces make a single topical point. All opinion articles appear online. Those selected to appear in print receive a DOI and PubMed indexed.

Word count

600 words and 10 references (800 words for blogs)

4.8 BMJ CAREERS

If you have an idea for an article about doctors' careers, please pitch it to us by emailing Tom Moberly (tmoberly@bmj.com). Send a few sentences explaining what you'd like to write about, how you'd like to cover the topic, and what you think readers would gain from the article you are proposing. If we like your idea we will contact you to discuss how we would like to proceed.

4.9 FILLERS AND ENDPieces

These are short articles that aim to entertain readers and make them think. Originally evolving to fill a gap in the print version of *The BMJ*, accepted submissions are now published online, and some are chosen to appear in print.

We welcome submissions on topics such as:

- A patient who changed my practice;
- A memorable patient;
- A paper that changed my practice;
- The person who has most influenced me;
- My most informative mistake;
- A story conveying instruction, pathos, or humour.

Word count

To be suitable for print, Fillers must be less than 300 words. Endpieces are quotations of no more than 80 words (often fewer) from any source.

4.10 OBITUARIES

We welcome obituaries for doctors with a connection to the UK within a year of their death. Please send your copy as a Word file to obituaries@bmj.com. We assume that material is sent exclusively to us, and we publish the full versions we receive on [bmj.com](#). We produce the short obituaries in the print issue from these full versions; these usually appear with a time lag of several weeks.

Obituaries include mandatory biographical details: the last position held, date of birth, place and year of qualification, postgraduate qualifications if applicable, and date and cause of death. Pictures should be sent as high—resolution images electronically or as photographs. We do not accept obituaries sent by post or handwritten obituaries. Please include a postal address if you want us to send one a copy of the relevant print issue to the families of the deceased (additional copies will have to be purchased from support@bmj.com).

We generally commission the full page obituaries for the print issue of *The BMJ* from professional writers: these are usually about doctors and are published no more than three months after death. We regret that we cannot provide individual progress updates. NB: Obituaries are not indexed in PubMed.

Word count

Around 150 words

Examples of other articles

The best way to get a feel for the different article types we publish is to look at a selection of our recently published content. Below you can find links to all content described on this page

[Editorials](#)

[Personal views](#)

[BMJ Opinion](#)

[BMJ Careers](#)

[Fillers and endpieces](#)

The BMJ submission system
You can submit articles using our system by visiting submit.bmj.com

5.1 SUBMITTING AN ARTICLE

Once you have read all of the above advice for your article type, and prepared your article, it's time to submit. Not all articles require submission through our submission system (some use a pitch form system), so please ensure you have taken note of this above before proceeding.

At *The BMJ*, we use a system called ScholarOne to manage our submission processes. Essentially, ScholarOne will convert your manuscript to a PDF for the review process. Most common word processing formats are accepted for text and tables, although the system prefers Microsoft Word, and images should be submitted as GIF, TIFF, EPS, or JPEG files.

The system can also accept supplementary files (for example: videos, datasets, research protocols, and checklists or statements), related articles published or available elsewhere, articles in press elsewhere, permission letters, etc. These are files that normally do not appear with the print article, although they might accompany the final version of the paper online. Supplementary files are not converted to PDF but will be available to reviewers or editors exactly as you upload them.

Registration

To access the system for the first time you will need to register [here](#). Please follow the "Register here," link in the right hand grey column. You will be asked to complete three steps:

- Name and email information;
- Address information;
- User ID and password;
- Your job description, specialty and marketing preferences should also be filled in on this page.

If you would like to be considered as a reviewer for *The BMJ* please also fill in your expertise terms. Anyone can respond without a subscription to any article published on *The BMJ* by sending a rapid response.

The submission process

We offer a step by step guide to submission on our website, available on our [Author Submission pages](#).

Detailed help files are available throughout our online editorial office and can be used without stopping the submission process. If you experience serious problems please email *The BMJ*'s editorial office at papersadmin@bmj.com

6.1 RAPID RESPONSES

What are rapid responses?

Anyone can respond without a subscription to any article published on *The BMJ* by sending a rapid response.

Rapid responses are electronic letters to the editor. Our weekly letters are edited selections of posted rapid responses and are indexed in PubMed. Rapid responses are not indexed in PubMed but they have their own URL and are retrievable in an advanced search of thebmj.com in perpetuity. Thus a rapid response is published with its first appearance online.

As an author, what should I know about rapid responses?

The corresponding author of every article in *The BMJ* receives an automated email when the paper is published online, and an automated reminder whenever a rapid response is posted to the article on thebmj.com. Given that authors have an academic duty to respond to substantive criticism of their work, *The BMJ* [expects authors to post their own rapid responses on bmj.com in reply to any such substantive comments](#), and editors may send reminders about this.

How to send rapid responses?

When you have found the article on thebmj.com that you would like to respond to, click on "Respond to this article" in the "Article Tools" section.

Fill in the form, typing or cutting and pasting your rapid response into the larger box under "Compose your response"; using the smaller box for the response title.

Accept the terms and conditions, and type the jumble of letters and numbers that you can see into the final box; these characters have been generated automatically as a spam filter to determine whether you are human or machine.

Click on 'Submit rapid response.' You should then get a message on the screen thanking you for sending your response, as well as an automatic acknowledgement to your email address. These two measures confirm that your rapid response has arrived at thebmj.com to be considered for posting.

Terms and conditions for rapid responses

We have a wide list of terms and conditions for rapid responses, applicable for both authors and readers. Read our full list of T&Cs online at our [Resources for Readers](#) pages.

FURTHER INFORMATION FOR AUTHORS

Although this document covers a large swathe of the article production and submission process at *The BMJ*, we offer a fully comprehensive guide for authors at our website, available at bmj.com/about-bmj/resources-authors

Read about our publishing model in detail at bmj.com/about-bmj/publishing-model

Read about our [ethics and policies](#) and our [complaints procedure](#)

For any further queries, please contact papersadmin@bmj.com